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CADTH COMMON DRUG REVIEW

Clinical Review Report

Nusinersen (Spinraza)

(Biogen Canada Inc.)

Indication: Treatment of patients with 5q SMA

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Abbreviations

ACEND	Assessment of Caregiver Experience in Neuromuscular Disease
AE	adverse event
ASO	antisense oligonucleotide
BiPAP	bi-level positive airway pressure
CDR	CADTH Common Drug Review
CI	confidence interval
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
EQ-5D	EuroQol 5-Dimensions
HFMSE	Hammersmith Functional Motor Scale – Expanded
HINE	Hammersmith Infant Neurological Examination
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
ITT	intention-to-treat population
MCID	minimal clinically important difference
mg	milligram
mL	millilitre
PedsQL	Pediatric Quality of Life Inventory
PP	per-protocol
RULM	Revised Upper Limb Module
RWC	real-world care
SAE	serious adverse event
SD	standard deviation
SMA	spinal muscular atrophy
SMN	survival motor neuron
WDAE	withdrawal due to adverse event
WHO	World Health Organization

Drug	Nusinersen (Spinraza)
Indication	Treatment of patients with 5q Spinal Muscular Atrophy (SMA)
Reimbursement Request	Treatment of patients with 5q Spinal Muscular Atrophy (SMA)
Dosage Form(s)	5 mL solution for intrathecal injection administered in four loading doses (days 0, 14, 28, and 63) followed by maintenance treatment of 5 mL solution every four months
NOC Date	June 29, 2017
Manufacturer	Biogen Canada Inc.

Executive Summary

Introduction

Spinal muscular atrophy (SMA) is a severe neuromuscular disease and is the leading genetic cause of infant death. It is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness. Neurological studies indicate that the disease causes a rapid and irreversible degeneration of motor neurons. The rate of motor neuron degeneration has been reported to plateau with time. The most common form of SMA, 5q SMA, makes up more than 95% of all cases and is an autosomal recessive disorder caused by homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (SMN1) gene.[1,2] While deletion or mutation of the SMN1 gene results in survival motor neuron (SMN) protein deficiency (which is essential for the development of motor neurons), the survival motor neuron 2 (SMN2) gene produces a relatively small amount of functional SMN protein and SMN2 copy number modulates the severity of the disease. SMA is a rare disease and estimates of its incidence and prevalence vary between studies. The incidence of SMA is often cited as being approximately 10 in 100,000 live births. Incidence and prevalence estimates in Canada are not well described in the literature. However, the manufacturer of nusinersen provided Canadian figures of an annualized estimate of new cases of SMA in Canada at 37.2 new cases per year. Four clinical subtypes of SMA are described. SMA type I makes up about 60% of SMA diagnoses where patients show symptoms before 6 months of age, never achieve the motor milestone of sitting unsupported, and generally do not survive past two years of age due to respiratory failure. Patients with SMA type II achieve the milestone of sitting unsupported, but never walk independently. Symptoms generally appear between 6 to 18 months after birth. Most patients will survive past the age of 25, with life expectancy improved by aggressive supportive care. SMA type III makes up about 10% to 20% of SMA cases and presents between 18 months of age and early adulthood. These patients are able to walk independently at some point in their life and typically have a normal life expectancy. SMA type IV constitutes a very small proportion of SMA cases, has an adult onset, and is the mildest form of the disease. Although muscle weakness is present, these patients retain the ability to walk, have a normal life expectancy, and do not suffer from respiratory or nutritional issues.

Aside from the reviewed drug, there are currently no treatments available for SMA. Standards of practice revolve around supportive care, addressing the symptoms of the disease, and attempting to improve quality of life. Nusinersen (Spinraza) is indicated for the treatment of 5q SMA. It is an antisense oligonucleotide (ASO) that increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts made, through binding to a specific site in the SMN2 pre-messenger ribonucleic acid. This leads to the translation of a specific site in the SMN2 pre-messenger ribonucleic acid into functional full-length SMN protein. Nusinersen is administered intrathecally by lumbar puncture in a 5 mL solution containing 12 mg of nusinersen. It is given in a regimen of four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a frequency of every four months.

Results and Interpretation

Included Studies

One phase III randomized, sham-controlled trial met the inclusion criteria for the CDR systematic review. The ENDEAR study (also known as CS3B) was a randomized, double-blind, sham-controlled, multi-centre study. One-hundred and twenty-one patients were randomized at a ratio of 2 to 1 to nusinersen (n = 80) or sham procedure (n = 41) arms. The study was designed to last for 13 months, with the double-blind treatment period lasting for 10 months and 3 months of follow-up. However, the double-blind period was concluded early after the results of the pre-specified interim analysis (6 months) suggested positive results. Two primary end points were assessed: proportion of Hammersmith Infant Neurological Examination (HINE) Section 2 responders, and time to death or permanent ventilation.

The main limitation of the ENDEAR study was the early termination of the study which caused loss of data and a shorter time period to assess the efficacy and safety of nusinersen. These two factors may have also contributed to a lack of statistical power necessary to capture differences in the secondary outcomes and subgroup analyses. The use of a non-intention-to-treat (non-ITT) population for the primary analysis, the lack of appropriate control for multiple statistical testing, and the potential for inadvertent unbinding of the investigator were additional limitations that may have had an impact on the interval validity of the ENDEAR trial. The external validity of the trial was limited by the inability to generalize the results to patients with infantile-onset SMA who had disease durations of more than 26 weeks, especially when considering the rapid and irreversible loss of motor function early in the disease course. Further, patients with infantile-onset SMA who have three copies of the SMN2 gene are not represented in the ENDEAR study. These patients may show a varying degree of disease presentation and can fall into either a SMA type I or II categories.

Efficacy

The final analysis demonstrated that the difference in the proportion of HINE Section 2 motor milestone responders favoured the nusinersen treatment group over the sham procedure control group (difference in percentage = 50.7, 95% CI, 31.8 to 66.5, *P* value < 0.0001). This indicated that almost half of the patients in the nusinersen group were able to exhibit more improvements than worsening in the milestones outlined in the HINE Section 2, with the exception of voluntary grasp. Several sensitivity analyses using different definition of responders and different analysis sets support the primary analysis. When

analyzing this outcome in subgroups of patients that had a disease duration 12 weeks or less and patients with disease duration of more than 12 weeks, a statistically significant difference was found in both groups. However, results of the subgroup analyses are considered exploratory as these were outside of the stage-wise hierarchical strategy and, therefore, not adjusted for multiplicity. The captured improvements in motor milestones of patients was also supported by a second motor milestone measure, the CHOP INTEND, where 71% of the patients allocated to nusinersen treatment achieved an improvement of 4 or more points on the CHOP INTEND scale as compared with 3% in the sham procedure control group (percentage difference = 68.53, 95% CI, 51.27 to 81.99). The main analysis of the second primary outcome, time to death or permanent ventilation, indicated that 39% of patients in the nusinersen group died or required permanent ventilation compared with 68% of patients in the sham procedure group during the analysis period (hazard ratio [HR] = 0.53, 95% CI, 0.32 to 0.89). Median survival time was unavailable for the nusinersen group, as an insufficient number of patients had completed the full trial. Median survival time for the sham group was 22.6 weeks (95% CI, 13.6 to 31.3). A subgroup analysis based on the median disease duration (less than and equal to 12 weeks, greater than 12weeks), showed statistically significant differences compared with the sham procedure group for the subgroup of patients with disease duration less than and equal to 12 weeks (HR = 0.24, 95% CI, 0.10 to 0.58) but failed to show statistically significant differences for the subgroup of patients with median disease duration of greater than 12weeks (HR = 0.84, 95% CI, 0.43 to 1.67). Moreover, when broken down to each event type separately, the results indicate a statistically significant difference between nusinersen group and the sham procedure in overall survival (HR = 0.37, 95% CI, 0.18 to 0.77), but not in time until permanent ventilation (HR = 0.66, 95% CI, 0.32 to 1.37).

Efficacy results from the supportive evidence is limited due to either study design (single-arm, non-comparative, descriptive, or phase II), or the use of a treatment regimen and/or dose that was not approved by Health Canada, or a combination of both factors. Presymptomatic patients who received nusinersen treatment in the NURTURE trial showed no fatalities after six months of assessment. Study CS3A indicated that patients with infantile-onset symptomatic SMA show improvement in motor milestone development while treated with nusinersen; two patients (13%) died in the period of the study (728 days). In the CHERISH trial, nusinersen-treated patients with childhood-onset SMA exhibited a statistically significant gain in motor function compared with patients in the sham control group.

Harms

Adverse events were reported in 96% of patients in the nusinersen group and 98% in the sham control group. Most adverse events and serious adverse events (SAEs) were related to infections and respiratory related complications. A number of patients (5%) in the nusinersen arm experienced vomiting, while none in the sham group did. A lower percentage of SAEs was reported in the nusinersen arm (76%) than in the sham procedure arm (95%). Withdrawals due to adverse events (WDAE) were reported in 16% of nusinersen-treated patients and 39% of patients in the sham control group; all withdrawals due to adverse events were due to the death of the patient. Causes of death related to respiratory failure or arrest represented more than half of the cases. Extension and long-term safety data studies have reported a similar safety profile.

Potential Place in Therapy[1]

SMA results in the irreversible loss of motor neurons and motor nerves. The loss of these nerves causes skeletal muscles to become progressively weaker giving rise to swallowing problems and breathing difficulties and/or weakness of the limbs and trunk. A natural history study using a specialized neurophysiological technique called motor unit number estimation (MUNE) has found that there is a relatively rapid loss of motor neurons early in the course of the disease followed by a more gradual decline.[3] As such, the optimal time for intervention is early in the course of the disease before this rapid and irreversible loss of motor neurons has occurred.

SMA is diagnosed in Canada via genetic testing. Initial testing evaluates for the homozygous 5q deletion within the survival motor neuron 1 gene (SMN1) which identifies 95% of cases. If negative, SMN1 gene sequencing will be performed as a second step. Nerve conduction studies and electromyography (EMG) is performed in a subset of patients, however even when evidence of a motor neuronopathy is identified on this study it is followed up with confirmatory genetic testing.

Current standard of care practice for patients with confirmed SMA include surveillance and anticipatory management ensuring that patients receive monitoring of: 1) growth, gastrointestinal function and nutrition; 2) respiratory complications and; 3) orthopedic complications (i.e., scoliosis and/or contractures).[4] Anticipatory management of respiratory complications are particularly important for children with SMA type I and II since these patients are at high risk of having a weak cough with impaired clearance of airway secretions; nocturnal hypoventilation and; recurrent pulmonary infections. This standard of care is not expected to change with emerging therapies, however it is hoped that the progression and complications of this disease may be lessened.

Nusinersen is the only Health Canada–approved treatment that is available for children with SMA. Treatment is administered via intrathecal injection and has been shown to be safe in several clinical trials.[5,6] There is convincing evidence that nusinersen is effective for children with SMA type I. This includes both early, asymptomatic infants with SMA type I (NURTURE study) and young (less than 7 months old) symptomatic infants with SMA type I (ENDEAR study).[5,6] Treated infants show improved survival (compared with natural history data) as well as improvement in their gross motor development as measured by the HINE. Clinical improvement was even more pronounced when infants were treated earlier, particularly when presymptomatic.[5] According to the clinical expert consulted for this review, given these results, nusinersen should be available for all Canadian infants with SMA type I. Knowing that presymptomatic treatment with nusinersen offers the greatest potential for preventing irreversible loss of motor neurons, physicians and public health agencies must consider what can be done to ensure early diagnosis including the potential for including SMA into provincial newborn screening programs.

Nusinersen has also demonstrated efficacy for children (aged 2 years to 12 years) with SMA type II (CHERISH study). The interim results of a placebo-controlled trial identified children to show an improvement in motor strength and function as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE. Since children's muscle fibres undergo an increase in size over the first few years of life (a process known as physiological hypertrophy), any intervention to prevent the irreversible loss of motor neurons and consequently, allow muscle fibres the potential to more normal development

1 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

is advantageous. Early recognition and treatment is also important in this group. Although nusinersen has not been well studied in children with SMA type III, it would be predicted that children in this group would have a greater potential for increasing SMN protein, if treated early in the course of their disease. Patients with SMA type III comprise about 10% to 20% of all patients with SMA. These children have had the ability to walk at some point although this can be lost as the disease progresses. Early treatment of patients with SMA type III, particularly young patients with apparent rapid disease progression would have the theoretical potential of preventing loss of ambulation with the significant gain of independence and avoidance of numerous medical complications that can result in non-ambulatory patients.

Conclusions

One randomized, double-blind, sham-controlled trial (ENDEAR, N = 121) met the inclusion criteria of the CDR systematic review. Patients included in the ENDEAR trial had a confirmed diagnosis of SMA, were less than seven months or age, had only two copies of the SMN2 gene, had a disease duration of no more than 25.86 weeks, and were most likely to develop SMA type I. Patients were randomized in a 2:1 ratio to nusinersen treatment or a sham control group. Patients were to receive ten months of treatment and have an additional three months of follow-up, however, the ENDEAR trial was concluded early, based on positive results from a pre-planned interim analysis. There were statistically significant differences between the two groups in favour of the nusinersen group, for both co-primary end points in the ENDEAR trial: the proportion of motor milestone responders as assessed by the HINE Section 2 tool, and the time to death or permanent ventilation. No adverse events in the ENDEAR trial were considered by the study investigators to be related to the study treatment. The percentage of patients experiencing SAEs and WDAEs were lower in the nusinersen treatment group versus the sham procedure arm. The main limitations of the ENDEAR trial was the early termination of the study which caused loss of data, a shorter time period to assess the efficacy and safety of nusinersen, and the inability to generalize the results to patients with infantile-onset SMA who had disease duration of more than 26 weeks.

Supportive evidence from two phase II trials (NURTURE, CS3A), one phase III trial (CHERISH), and two extension and long-term safety studies provided additional safety and efficacy data for patients who are likely to develop SMA type I and II. Presymptomatic patients who received nusinersen treatment in the NURTURE trial showed no fatalities after six months of assessment, while in the CHERISH trial, nusinersen-treated patients with childhood-onset SMA experienced a statistically significant gain in motor function compared with patients in the sham control group. No new safety signals were identified in any of the supporting studies. These studies, however, were limited due to study design (single-arm, non-comparative, descriptive, or phase II), and/or the use of a treatment regimen or dose that was not approved by Health Canada.

Table 1: Summary of Results

	ENDEAR	
HINE Section 2 Motor Milestone Responders	**Nusinersen**	**Control**
Number of patients, N	73	37
Motor milestone responders[a], N (%)	37 (51)	0
Difference in percentages (95% CI)	50.7 (31.8, 66.5)	
P value	< 0.0001	
Time to death or permanent ventilation		
Number of patients, N	80	41
Number of patients who died or required permanent ventilation, n (%)	31 (39)	28 (68)
Estimated proportion of patients who died or required permanent ventilation by:		
Day 91 (13 wks/3 mos)	0.24	0.27
Day 182 (26 wks/6 mos)	0.29	0.61
Median survival time (wks), median (95% CI)	NA (36.3 to NA)	22.6 (13.6 to 31.3)
Day 273 (39 wks/9 mos)	0.40	0.70
Day 364 (52 wks/12 mos)	0.45	0.74
Day 394 (13 mos)	0.45	0.74
Hazard ratio (95% CI)	0.53 (0.32 to 0.89)	
P value	0.0164	
Serious adverse events		
Number of patients, N	80	41
Patients with > 0 SAEs, N (%)	61 (76)	39 (95)
Respiratory distress	21 (26)	8 (20)
Respiratory failure	20 (25)	16 (39)
Pneumonia	19 (24)	5 (12)
Atelectasis	14 (18)	4 (10)
Acute respiratory failure	11 (14)	9 (22)
Pneumonia aspiration	8 (10)	5 (12)
Rhinovirus infection	7 (9)	2 (5)
Respiratory tract infection	6 (8)	1 (2)
Cardiorespiratory arrest	5 (6)	5 (12)
Respiratory arrest	5 (6)	4 (10)
Viral infection	5 (6)	1 (2)

CI = confidence interval; HINE = Hammersmith Infant Neurological Examination; mos = months; N = total number of patients; n = number in subgroup; NA = not applicable; OR = odds ratio; SAE = serious adverse event; wks = weeks.

[a] Definition of a motor responder was: (i) the patient demonstrated at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND (ii) among the seven motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined in [i]) in more categories than worsening.

Introduction

Disease Prevalence and Incidence

Spinal muscular atrophy (SMA) is a severe neuromuscular disease and is the leading genetic cause of infant death.[7,8] It is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness.[8] Neurological studies indicate that the disease causes a rapid and irreversible degeneration of motor neurons, the rate of motor neuron degeneration has been reported to plateau with time.[3] The most common form of SMA, 5q SMA, makes up more than 95% of all cases and is an autosomal recessive disorder caused by homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (SMN1) gene.[1,2] SMN protein is essential for the development of motor neurons, and while deletion or mutation of the SMN1 gene results in SMN protein deficiency, the SMN2 gene produces a relatively small amount of functional SMN protein and SMN2 copy number modulates the severity of the disease.[1,7-9] SMA is a rare disease and estimates of its incidence and prevalence vary between studies. Most of these studies relied on clinical rather than genetic diagnosis and were often performed in small cohorts based in Europe.[2] The incidence of SMA is often cited as being approximately 10 in 100,000 live births.[2] One recent review found estimates ranging from 5.0 to 24 in 100,000 births.[2] Prevalence is estimated to be approximately one to two in 100,000 persons[2] and is affected by the drastically shortened life expectancy in the most common type of SMA. Incidence and prevalence estimates in Canada are not well described in the literature. However, the manufacturer of nusinersen provided Canadian estimate figures based on the average of three published studies of live birth incident rates in the US, Sweden, and Poland,[10-12] The manufacturer approximated the annualized estimate of new cases of all SMA subtypes in Canada at 37.2 new cases per year; with the highest estimate of new cases in the province of Ontario at 13.9 new cases per year, second is the province of Quebec at 8.2 cases per year, third is the province of Alberta at 5.5 cases per year, and fourth is the province of British Columbia at 4.2 new cases per year, the rest of the provinces had an estimate of less than two cases per year.[13]

The disease first manifests in various ways, depending on age of onset. Infants present with severe hypotonia and feeding difficulties while later onset in young children may appear as difficulty with stairs and frequent falls.[14] Adult-onset SMA presents as mild proximal muscle weakness.[8] Genetic testing gives a definitive diagnosis for 5q SMA and the first step is to test for SMN 1 gene deletion.[9] If homozygous SMN1 deletion is not found, sequencing of the SMN1 coding region may identify a causative mutation[9]. Genetic testing of the SMN2 gene can shed light on the potential subtype of SMA, as described below.

SMA is divided into four clinical subtypes (See Appendix 7 for an overview of the disease natural history):

Type I: These patients show symptoms before 6 months of age, never achieve the motor milestone of sitting, and generally do not survive past two years of age due to respiratory failure [1,7-9]. SMA type I is the most common type of SMA, accounting for about 60% of SMA diagnosed.[2] The manufacturer approximated the annualized estimate of new cases of SMA type I to be 22.9 new cases per year nationally.[13] Almost all SMA type I patients have two or three copies of SMN2, giving rise to a broad range of phenotypes.[15] Achievement of the

motor milestone of sitting independently may cause a patient who was classified as SMA type I to be reclassified as SMA type II.[3,15] Additional subtypes of IA, IB, and IC have been proposed based on age of onset with IA being the earliest and most severe subtype. SMA type 0 is sometimes included in classification systems and presents in neonates as joint contractures, severe weakness and hypotonia, respiratory insufficiency, and a life expectancy of less than six months.[1,7]

Type II: Patients with type II SMA achieve the milestone of sitting unsupported, but never walk independently. The manufacturer approximated the annualized estimate of new cases of SMA type II to be 10.5 new cases per year nationally.[13] Symptoms generally appear between 6 to 18 months after birth and most patients will survive past the age of 25,[7,14] with life expectancy improved by aggressive supportive care.[14] Type II patients represent about 20% to 30% of SMA cases[2] and most SMA type II patients have three copies of SMN2.[15] In addition to the inability to walk independently, common symptoms are fine tremors of the upper extremities, tongue fasciculation, joint contractures, and scoliosis.[1,9,14]

Type III: Type III SMA makes up about 10% to 20% of SMA cases[2] and presents between 18 months of age and adulthood. These patients are able to walk independently at some point in their life and typically have a normal life expectancy.[14] Most type III patients have three of four copies of SMN2.[15] An age of onset prior to 3 years is associated with estimated probabilities of 73%, 44%, and 34% of walking 10, 20, and 40 years after onset.[16] In those with age of onset after 3 years, the estimated probabilities are 97%, 89%, and 67% for walking 10, 20, and 40 years after onset.[16] SMA type III patients have little or no respiratory weakness.[1] Ambulatory patients may exhibit abnormal gait characteristics due to proximal weakness[14] while patients who lose the ability to walk often develop scoliosis.[9]

Type IV: A very small proportion of SMA cases are type IV or adult-onset SMA, the mildest form of the disease. Although muscle weakness is present, these patients retain the ability to walk, have a normal life expectancy, and do not suffer from respiratory or nutritional issues.[9]

Patient input for this review described the diagnosis of a child with SMA as having a devastating effect. The feeling of hopelessness and despair in the face of a progressive and severe illness is especially pronounced, considering the absence of effective therapies. Young patients miss out on typical childhood experiences such as using the playground. In more severe cases, patients cannot execute basic movements such as sitting up and require help with needs such as transfers as well as positioning in wheelchair and in bed. In the most severe cases of infantile-onset SMA, the condition worsens over time and the patient passes away before reaching their second birthday.

Standards of Therapy

Aside from the reviewed drug, there are currently no treatments available for SMA. Standards of practice involve best supportive care, addressing the symptoms of the disease, and attempting to improve quality of life. Respiratory management is essential for all children with type I SMA and some with type II. Non-invasive ventilation with bi-level positive airway pressure (BiPAP) can help with disordered breathing at nighttime and can be used during the day, as needed, for hypercapnia.[1] Secretion mobilization is also important in patients with weak cough and this can be achieved with postural drainage, assisted coughing, and oral suction.[7,9] When non-invasive ventilation is no longer sufficient, tracheostomy and permanent, invasive ventilation is an option. However, there is no

consensus in guidelines regarding the suitability of this intervention and its use remains a choice for the family.[7,14] In patients with difficulty chewing and swallowing, changing food consistency can help with feeding and reduce risk of aspiration. A gastrostomy tube can also be placed, although there is no consensus on when this should occur.[14]

For gross motor function, management strategies include mobility aids, bracing, and physical therapy. Patients able to bear weight may make use of a standing frame or ankle-foot orthoses and physical activity such as swimming can increase stamina.[14] Manual and motorized wheelchairs provide mobility to those who can use them. Scoliosis is very common in non-ambulatory patients with SMA type II and III, and can be corrected with surgery.[14] Bracing, seating modification, and physical therapy may slow scoliosis progression in a child until they can undergo surgery.[7]

Drug

Nusinersen (Spinraza) is indicated for the treatment of 5q SMA. It is an antisense oligonucleotide (ASO) that increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts made, through binding to a specific site in the SMN2 pre-messenger ribonucleic acid. This leads to the translation of the messenger ribonucleic acid into functional full-length SMN protein. Nusinersen is administered via intrathecal injection by lumbar puncture in a 5 mL solution containing 12 mg of nusinersen. It is given in a regimen of four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a frequency of every four months.[6]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of nusinersen for the treatment of patients with 5q SMA.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were also eligible for inclusion based on the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient Population	Patients with 5q SMA Subgroups: SMA type (type I, II, III, and IV) Disease duration
Intervention	Nusinersen 12 mg (5 mL) via intrathecal administration by lumbar puncture in four loading doses at day 0, day 14, day 28, and day 63, with subsequent maintenance doses at a frequency of every four months
Comparators	• Best supportive care • Placebo or sham • No treatment
Outcomes	**Key efficacy outcomes:** Motor function related outcomes: • Assessment of muscle strength and/or mobility using a validated scale[a] • Assessment of gross and fine motor skills development in pediatric population using a validated scale Respiratory related outcomes: • Assessment of pulmonary function[a] Survival related outcomes: • Overall survival • Event-free survival (e.g., invasive ventilation, hospitalization) Patient reported outcomes: • Health-related quality of life using a validated scale[a] • Assessment of symptoms severity using a validated scale[a] **Other efficacy outcomes:** • Caregiver burden • Use of respiratory or ventilatory assist devices • The need for enteral or parenteral feeding[a] • Weight percentile in pediatric population • Hospitalization **Harms outcomes:** • Adverse events, serious adverse events, withdrawals due to adverse events, mortality • Adverse events of special interest: serious infection, serious respiratory infection, respiratory complication related to drug anesthesia, lumbar puncture related adverse events (e.g., bleeding, brainstem herniation, meningitis, pain post lumbar puncture), coagulation abnormalities, renal toxicity
Study Design	Published and unpublished phase III randomized controlled trials

mg = milligrams; mL = millilitres; SMA = spinal muscular atrophy.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Spinraza and Nusinersen

No Methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on July 27, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on November 15, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Databases (free); Internet Search. Google and other Internet search engines were used to search for additional Web-based materials, including conference abstracts. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of 60 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

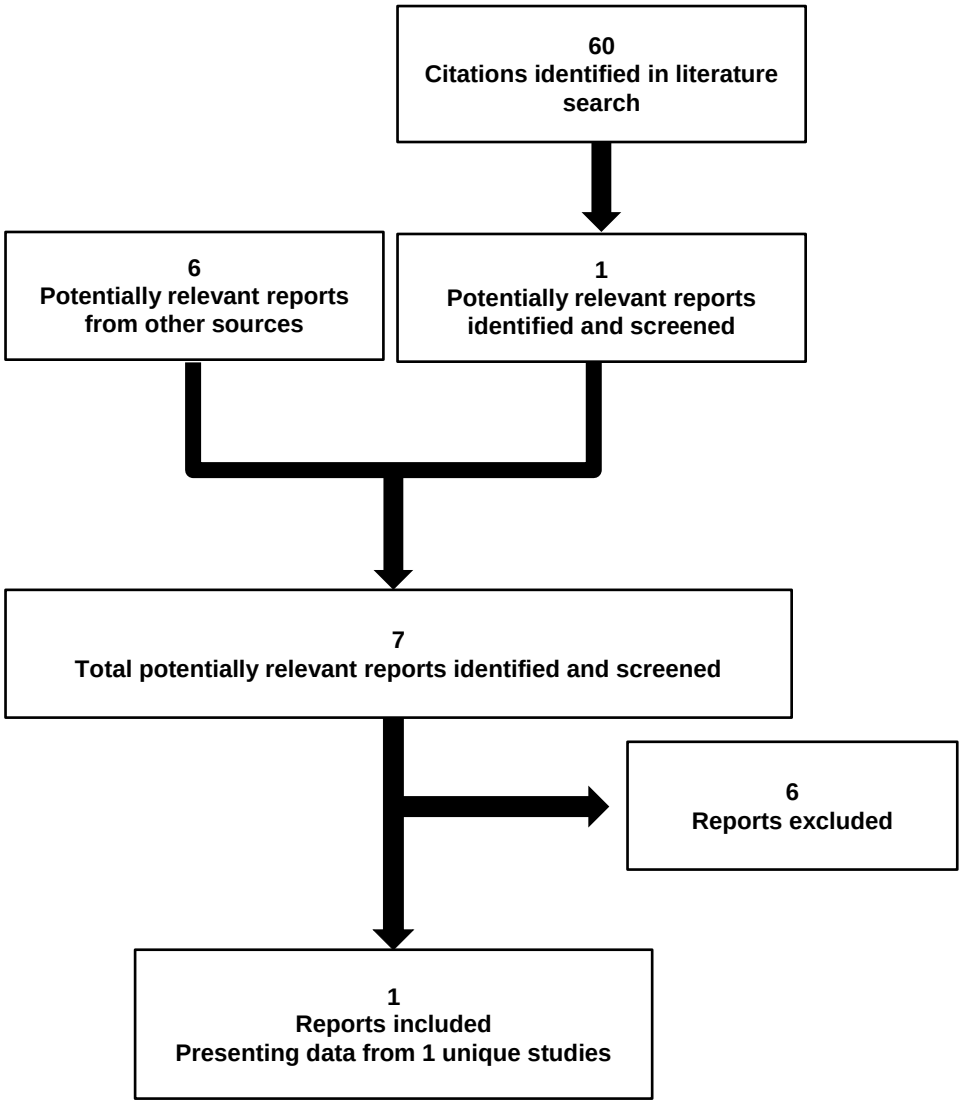


Table 3: Details of Included Study

		ENDEAR (CS3B)
Designs & Populations	**Study Design**	Phase III, randomized, double-blind, sham-controlled, multi-centre trial.
	Locations	North America (Canada and US), Europe, Asia-Pacific region.
	Enrolled (N)	121
	Inclusion Criteria	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote. • Genetic documentation of 2 copies of SMN2. • Onset of clinical signs and symptoms consistent with SMA at ≤ 6 mos (180 days) of age. • Males and females ≤ 7 mos (210 days) of age at screening. • Patients were the product of a pregnancy of 37 to 41 wks gestation.
	Exclusion Criteria	• Hypoxemia. • Signs or symptoms of SMA present at birth or within the first week after birth. • History of or active condition that would interfere with lumbar puncture or assessment of study. • Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.), biological agent, or device within 30 days prior to screening or anytime during the study. Any history of gene therapy, prior ASO treatment, or cell transplantation.
Drugs	**Intervention**	12 mg (in a 5-mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen administered via intrathecal injection by lumbar puncture on days 1, 15, 29, 64, 183, and 302.
	Comparator(s)	Sham procedure on days 1, 15, 29, 64, 183, and 302.
Duration	Screening	21 days
	Double-blind treatment period	10 mos
	Follow-up	3 mos
Outcomes	**Primary End Point**	• Proportion of HINE Section 2 motor milestone responders. • Time to death or permanent ventilation.
	Other End Points	• Proportion of CHOP INTEND responders • Survival rate • Proportion ventilation-free • Growth parameters • Hospitalization
Notes	**Publications**	"None"

ASO = antisense oligonucleotide; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF = cerebrospinal fluid; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; mos = months; N = total number of patients; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN = survival motor neuron; WHO = World Health Organization; wks = weeks.

Source: Clinical study report: ISIS 396443-CS3B.[17]

Included Studies

Description of studies

One phase III randomized, sham-controlled trial met the inclusion criteria in the CDR review protocol. The ENDEAR study (also known as CS3B) was a phase III randomized, double-blind, sham-controlled, multi-centre study, that included Canadian sites. Subsequent to screening assessment, patients were randomized on a 2:1 ratio to nusinersen or sham, respectively, using an interactive voice/ web response system. The unequal randomization ratio was justified on an ethical basis.[13,17] The randomization was based on a permuted block schedule and was stratified for disease duration (defined as the age of the patient at screening minus age at symptom onset) at 12 weeks or less or more than 12 weeks. To maintain blinding, dedicated study personnel administered the injection in an unblinded fashion in a dedicated room where key study personnel (i.e., the principal investigator, study coordinator, or outcomes assessors) were not present. The sham procedure consisted of a needle prick to the target area where the treatment would be administered, covered with the same bandage, and patients kept in the procedure room for the same amount of time. The sham kits were packed in a blinded fashion and contained an artificial cerebrospinal fluid to simulate the cerebrospinal fluid samples collected in nusinersen-treated patients.[13] The study was designed to last for 13 months, with the double-blind treatment period lasting for 10 months and 3 months of follow-up. However, the double-blind period was concluded early due to the positive results after the results were assessed at the pre-specified interim analysis (6 months). After this early termination, all patients were to receive nusinersen afterward. One primary end point (proportion of Hammersmith Infant Neurological Examination [HINE] Section 2 responders) was assessed at the pre-specified interim analysis. Subsequent to the decision to terminate the study early, the final analysis of the two primary outcomes (proportion of HINE Section 2 responders, and time to death or permanent ventilation) was conducted.

Populations

Inclusion and exclusion criteria

Patients included in the ENDEAR study were genetically documented with 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote; had only two copies of the SMN2 gene; and were younger than 7 months of age. These inclusion criteria were intended to enroll patients who would most likely develop SMA type I. The exclusion criteria of the study included hypoxemia at presentation, history of a condition that would preclude a patient from receiving lumbar puncture, and previous exposure to experimental SMA treatment.

Baseline characteristics

A total of 121 patients were randomized to the nusinersen treatment arm or control arm in the ENDEAR trial. Overall, 55% of the randomized patients were females, and 86% were Caucasian. The diagnosis of SMA was established at a median age of 13.1 weeks (range 0 weeks to 25.9 weeks), and the first dose of the treatment (or sham) was received at a median age of 175 days (range 30 days to 262 days). There were imbalances noted in some baseline characteristics between the treatment and the control group with respect to the mean age of screening, first dose, and diagnosis, which were higher in the control group than in the treatment group. There were also differences between the two groups in

characteristics related to the symptoms of the disease; with a 13% higher proportion of patients in the treatment group experiencing pneumonia or respiratory symptoms (35% versus 22%), and a 22% higher proportion of patients in the treatment group experiencing difficulty swallowing (51% versus 29%). Baseline values of HINE Section 2 characteristics were, overall, similar between groups, except in the categories of 'voluntary grasp' and 'no rolling.' The proportion of patients who were able to use the whole hand to grasp was numerically higher in the control group (73% in control group versus 63% in treatment group); while the proportion of patients who were unable to roll was numerically lower in the control group (88% in control group versus 99% in treatment group). It is noted that a numerically higher proportion of patients in the treatment group required ventilator support than in the control group (26% versus 15%).

Table 4: Summary of Baseline Characteristics

	ENDEAR	
	Nusinersen (N = 80)	**Control (N = 41)**
Demographics		
Age at screening, mean (SD)	147.2 (46.9) days	164.7 (48.5) days
Age at first dose of study treatment, mean (SD)	163.4 (49.6) days	180.5 (50.9) days
Female, n (%)	43 (54)	24 (59)
White, n (%)	68 (85)	36 (88)
Asian, n (%)	5 (6)	1 (2)
[redacted]	[redacted]	[redacted]
SMN2 copy number		
Two copies, n (%)	80 (100)	40 (98)
Three copies, n (%)	0	1 (2)
Four copies, n (%)	0	0
Unknown, n (%)	0	0
Disease history		
Time from disease onset to study screening (wks), mean (SD)	13.2 (5.5)	13.9 (5.7)
Age at symptom onset (wks), mean (SD)	7.9 (4.0)	9.6 (4.7)
Age at diagnosis (wks), mean (SD)	12.6 (6.6)	17.5 (7.5)
Disease symptoms		
Hypotonia, n (%)	80 (100)	41 (100)
Developmental motor delay, n (%)	71(89)	39 (95)
Paradoxical breathing, n (%)	71(89)	27 (66)
Pneumonia or respiratory symptoms, n (%)	28(35)	9 (22)
Limb weakness, n (%)	79 (99)	41 (100)
Swallowing or feeding difficulties, n (%)	41(51)	12 (29)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	ENDEAR	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Disease supports		
Ventilatory support required, n (%)	21 (26)	6 (15)
[redacted]	[redacted]	[redacted]

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = Hammersmith Infant Neurological Exam; N = total number of patients; n = number of patients in subgroup; NR = not reported; SD = standard deviation; wks = weeks.

Source: Clinical study report: ISIS 396443-CS3B.[17]

Interventions

Patients enrolled in the ENDEAR study were randomized to either a scaled equivalent of 12-mg dose nusinersen treatment or sham injection based on the patient's age (the scaling of nusinersen is outlined in Table 5). The aim of adjusting the dose and volume was to achieve the same dose effect while accounting for the smaller cerebrospinal fluid volume. Nusinersen was administered using a single intrathecal injection through lumbar puncture using a spinal anesthesia needle and a 5-mL syringe, delivered as a slow bolus at the L3/L4 spinal space (plus or minus one lumbar spine level if needed). The treatment was administered according to a loading schedule (on study days 1, 15, 29, and 64) and a subsequent maintenance schedule of once every 4 months (on study days 183 and 302).

The sham procedure matched the dosing and the maintenance schedule of nusinersen treatment. It consisted of a needle prick, breaking the skin, at the site of an L3/L4 lumbar puncture. Patients were kept in the procedure room for the same duration of time as the nusinersen-treated patients, and the needle prick site was covered by the same bandage. The administration of both procedures was conducted by unblinded personnel in an enclosed procedure room where study investigators and parents were not allowed.

Concomitant medications were allowed as necessary to address any adverse events or to provide supportive care, as deemed necessary by the treating physician. Only experimental treatments for SMA were prohibited (e.g., salbutamol, valproate, creatine, and hydroxyurea).

Table 5: Scaling of Nusinersen Dose by Age

ENDEAR		
Age	**Dose**	**Volume of Injection**
0 – 3 mos	9.6 mg	4.0 mL
3 – 6 mos	10.3 mg	4.3 mL
6 – 12 mos	10.8 mg	4.5 mL
12 – 24 mos	11.3 mg	4.7 mL
> 24 mos	12 mg	5.0 mL

mg = milligrams; mL = millilitres; mos = months.

Source: Clinical study report: ISIS 396443-CS3B.[17]

Outcomes

Details regarding the validity and reliability of outcomes measure are presented in Appendix 5

a) Proportion of motor milestone responders (Section 2 of the HINE)

The proportion of HINE Section 2 responders was the first of two primary outcomes. The Section 2 of the HINE scale is concerned with motor milestones and assesses eight motor milestones: head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking.[18] Each milestone has three to five possible descriptive ratings, ranging from 'not performing the task at all' to 'fully demonstrating the milestone'.[18]

Although the original HINE developers did not define a quantitative scoring system for Section 2, scores for each milestone were obtained by assigning a value of 0 to the absence of the activity and adding 1 point for each incremental rating.[19] Specifically, a 1-point increase from baseline can be achieved if an improvement took place in any of the categories of head control, rolling, sitting, crawling, standing, or walking, a 2-point improvement is achieved through exhibiting the ability to kick or touch toes. Voluntary grasp was excluded from the analysis. The manufacturer indicated that it was excluded because voluntary grasp lacks movement against gravity, and many infantile SMA patients would achieve all milestones in this category.[20] Worsening was considered as at least a 2-point decrease or a decrease to the lowest possible level, no kicking in the ability to kick category, and at least a 1-point decrease for the other categories. Although a total score was not described in the original development of the tool, it is assumed by the reviewer that a total HINE score for Section 2 was calculated by scoring each milestone on an ordinal scale (with 0 representing no ability) and summing the scores. The manufacturer provided the following definition for motor milestone responders:

> "The definition of a motor milestones responder was based on the motor milestones categories in Section 2 of the HINE (with the exclusion of voluntary grasp) using the assessment at the later of the Day 183, Day 302, or Day 394 Visits as follows:
>
> (i) The patient demonstrated at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing, or walking, AND
>
> (ii) among the 7 motor milestone categories (with the exclusion of voluntary grasp), the patient demonstrated improvement (as defined in [i]) in more categories than worsening. Note: for the category of ability to kick, similar to the definition of improvement in (i) above, worsening is defined as at least a 2-point decrease or decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least a 1-point decrease."[17]

A minimal clinically important difference (MCID) score was not specifically identified from the literature for this measure. Although, the manufacturer reported that based on the natural history of SMA type I, a change in score of greater than 1 point for any given milestone is highly unlikely in untreated SMA type I patients.

Patients were assessed by a neurologist at the study centre, the assessment was performed at screening, and before the lumbar puncture procedure on study days 64, 183, 302, and 394.

b) Time to death or permanent ventilation

Time to death or permanent ventilation was the second primary outcome reported in the ENDEAR study. Permanent ventilation was defined in the study as the need for 16 hours or more of continuous ventilatory support per day for 21 or more consecutive days, in the absence of an acute reversible event, or the patient required tracheostomy. A patient's ventilation use was recorded daily by the caregiver and collected during study visits and weekly telephone contacts. The time to death or permanent ventilation was assessed by an adjudication committee blinded to the patient's assignment.

c) Proportion of Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) responders

A secondary outcome, the CHOP INTEND was developed in SMA type I infants and designed for use to measure motor function in infants and children with neuromuscular disorders.[21] It is made up of 16 items, each rated 0 to 4 (no response, minimal, partial, nearly full, and complete level of response) giving a maximum total score of 64 when summed with higher scores indicate better performance.[21]

The manufacturer defined a CHOP INTEND responder was defined in the study as a patient with a score change from baseline of 4 or greater points when assessed on study days 183, 302, or 394.

An MCID was not found for the CHOP INTEND score.

d) Survival rate

Overall survival of patients was a secondary outcome in the ENDEAR study.

e) Per cent of patients not requiring permanent ventilation

The percentage of patients who did not need permanent ventilation was reported as a secondary outcome in the ENDEAR study.

f) Growth parameters

Growth parameters was a tertiary outcome, where trained staff would assess weight, body length, arm circumference, chest circumference, and head circumference at screening and before the lumbar puncture on study days 29, 64, 183, 302, and 394. A growth failure was captured using two definitions: the first a post-baseline weight below the 5th percentile, and the second a weight drop crossing 2 or more major percentiles in six months.[17]

g) Hospitalization

The number of hospitalizations that occurred during the study period was measured as a tertiary outcome.

h) Drug-related adverse events and serious adverse events

An adverse event was recorded as "treatment emergent" if it either; existed before the first procedure and worsened subsequently, or if it was not present before the first procedure and subsequently appeared.

Statistical Analysis

ENDEAR was a randomized, double-blind, sham-controlled, clinical trial. [redacted]

At the interim analysis, only the motor milestone primary outcome was to be tested. [redacted] The outcomes hierarchy was according to the following:

1) Second primary efficacy end point, time to death or permanent ventilation.
2) The proportion of CHOP INTEND responders.
3) Time to death.
4) Percentage of patients not requiring permanent ventilation.
5) Proportion of compound muscle action potential (CMAP) responders.
6) Time to death or permanent ventilation in subgroup of patients with disease duration at screening below or at study median.
7) Time to death or permanent ventilation in subgroup of patients with disease duration at screening above study median.

[redacted]

[redacted]Two subgroup analyses in the first primary outcome of motor milestone responders were conducted based on the cut-off of the median disease duration of 12 weeks.

The analysis of the differences in the two groups for the second primary end point (time to death or permanent ventilation) was conducted using the log-rank test stratified by disease duration at screening (less than and equal to 12 weeks or greater than 12 weeks), [redacted]

[redacted]

[redacted]

Analysis populations

According to the previously described method of assigning study days for the premature end-of-study visit, the following analysis population was defined:

ITT Set: All patients who were randomized and received at least one dose of study treatment/sham procedure. Patients were analyzed in the treatment group to which they were randomized. [redacted]

Efficacy Set: All patients with a recorded study visit on day 183, 302, or 394 [redacted]

[redacted]

Safety Set: All patients who were randomized and received at least one dose of study treatment/sham procedure.

Patient Disposition

Table 6 summarizes the disposition of enrolled patients. By the time the study was prematurely terminated, 31% of patients had completed the full length of the study including the follow-up and 40% had completed the double-blind treatment period. The proportion of patients that completed the study in the nusinersen group was higher than in the control group.

Table 6: Patient Disposition

	ENDEAR	
	Nusinersen	**Control**
Screened, N	149	
Randomized, N (%)	81	41
Withdrawal prior to dosing, N	1	0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ITT, N (%)	80 (99)	41 (100)
Interim efficacy set, N (%)	51 (63)	27 (66)
Efficacy set, N (%)	73 (90)	37 (90)
[redacted]	[redacted]	[redacted]
Safety, N (%)	80 (99)	41 (100)

ITT = intention-to-treat; N = total number of patients; PP = per-protocol.

[a] No SAE was determined to be related to study treatment

Source: Clinical study report: ISIS 396443-CS3B.[17]

Exposure to study treatments

Table 7 summarizes treatment exposure. As of the data cut-off date, 73 patients out of the 80 that were allocated to the nusinersen treatment arm (91%) received at least four doses, 32 (40%) received all six doses. In the sham group, 34 (83%) had four sham procedures, and 14 (34%) underwent all six sham procedures.

Table 7: Exposure to Study Treatment

	ENDEAR	
	Nusinersen	**Control**
Number of patients, N	80	41
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	ENDEAR	
	[redacted]	[redacted]
Number of patients on study for, n (%)		
≥ 29 days (4 wks)	79 (99)	39 (95)
≥ 64 days (9 wks)	74 (93)	36 (88)
≥ 99 days (14 wks)	71 (89)	31 (76)
≥ 141 days (20 wks)	65 (81)	25 (61)
≥ 183 days (26 wks)	58 (73)	23 (56)
≥ 218 days (31 wks)	49 (61)	19 (46)
≥ 260 days (37 wks)	41 (51)	18 (44)
≥ 302 days (43 wks)	36 (45)	15 (37)
≥ 344 days (49 wks)	31 (39)	14 (34)
≥ 393 days (56 wks)	22 (28)	10 (24)

N = total number of patients; n = number of patients in subgroup; SD = standard deviation; wks = weeks.

Source: Clinical study report: ISIS 396443-CS3B[17]

Critical Appraisal

Internal validity

ENDEAR was a randomized, sham-controlled, double-blind, clinical trial. The study methods were generally well-reported (as summarized above), including the details of power analysis, randomization, allocation concealment, and statistical analysis. Overall, potential issues pertaining to the internal validity of the study can be identified as relating to the following points:

1) Unequal randomization ratio:

The manufacturer randomized patients in a 2:1 ratio to nusinersen or sham procedure, respectively. An ethical rationale for this approach was provided. Potential challenges that may be associated with such allocation ratio include the need for larger sample size to capture differences in treatment effect, and the potential of reducing the effectiveness of blinding as investigators and assessors would be aware that the probability of being allocated to active treatment is twice that of control.[22] Based on the primary end points of the study, it appears to be adequately powered given that statistically significant differences were observed.

A reduction in statistical power due to the 2:1 randomization ratio could potentially have an effect on the secondary outcomes and subgroups analyses.

2) Imbalances in the baseline patient characteristics after randomization between treatment groups:

Patients that were randomized to the sham procedure were older than patients randomized to the nusinersen group in terms of age at screening and age at first dose. Patients allocated to the treatment group had disease onset at a younger age, had 13% higher proportion of experiencing pneumonia or respiratory symptoms, 22% higher proportion experiencing difficulty swallowing, and a higher percentage of patients in the treatment group required ventilator support than in the control group (26% versus 15%). While this could bias the result in favour of the sham procedure, as patients in the nusinersen group were at higher risk of pulmonary complications, it is also possible that these patients may

have a greater potential to improve. As such, a definitive direction of this potential bias remains unclear.

3) Potential for investigators to unmask patients assignment:

While allocation concealment was maintained by including a sham procedure, there was a potential for treatment status to be unmasked post-randomization. It is possible that investigators who had previous experience caring for or researching SMA could ascertain treatment assignment in patients who exhibited considerable improvements in motor milestone development that are otherwise unlikely to be observed in untreated patients.[20] It is unclear if potential unblinding would introduce operational bias into the subsequent conduct of the study.

4) Premature termination of the study:

Since the study was prematurely concluded, only one-third of the population completed the full study length with the follow-up period. The missing data can be viewed as largely a result of late enrolment relative to the interim analysis date. In light of the positive interim analysis results and the severity of the disease, a decision to prematurely terminate the study and allow all patients to receive the active drug was made for ethical reasons. However, the data loss due to this premature cut-off may affect our ability to draw insight from secondary and subgroup analysis due to the smaller sample size than originally planned. Further, the premature cut-off reduced the available data for the second primary outcome in that the median time to death or permanent ventilation in the treatment group was not reached, despite the study being originally powered to double the median time to death or permanent ventilation. As well, premature termination of the study reduces the amount of longer-term safety data relative to a control group.

5) First primary outcome not using an ITT population:

The analysis of the first primary outcome (HINE Section 2 motor milestone responders), as well as the secondary outcome (CHOP INTEND), was based on an “efficacy population.” One aspect of this population is a complex process of handling missing data and varying study visit dates as end dates. However, the manufacturer provided several sensitivity analyses testing different approaches to handling missing data. This seemed also the conclusion reached in the FDA statistical review report.[23]

6) Lack of valid statistical inference for outcomes in the hierarchy after a non-significant result:

To control for multiple outcome testing, the manufacturer established a hierarchy for all secondary outcomes assessed. Statistical testing should have been stopped after the first non-statistically significant outcome was established. All outcomes that are lower on the hierarchy than the first non-significant outcome should be treated as nominal in nature.

7) Variation in use than original design of the HINE Section 2 tool:

The manufacturer used a summary score of the HINE Section 2 tool while excluding the section of voluntary grasp. The psychometric properties of the HINE Section 2 summary score in this form have not been characterized extensively. The summary score with all the milestones demonstrated acceptable test-retest reliability and moderate correlations with measure of motor function in a sample of 19 patients with SMA type 1.[24] A natural history study in 33 SMA type I patients observed only one occurrence of milestone improvement,

which was a 1-point improvement in the ability to kick.[19] While the available evidence supports a 1-point (2-point for ability to kick) increase as the threshold for improvement in this population, motor milestone responder as defined in the ENDEAR study has not been thoroughly evaluated as an outcome measure.

External validity

The ENDEAR study included two Canadian sites, and according to the clinical expert consulted for this review, the inclusion and exclusion criteria of the study were reasonable, and the patients enrolled in the ENDEAR trial are representative of patients typically seen in clinical practice who are likely to develop infantile-onset SMA type I. [redacted] This may indicate that there are likely several patients with SMA that do not meet the inclusion and exclusion criteria of the study, and the efficacy of nusinersen in such population is unknown. In addition, it is possible that the requirement of patients to have two copies of SMN 2 gene may have excluded a small proportion of patients that exhibit the phenotype of SMA type I but carry three copies of the SMN 2 gene. According to the clinical expert, the control group was also considered appropriate as standard and supportive care were allowed in the sham procedure group and there is lack of any effective therapy beyond supportive care.

Based on input from the clinical expert consulted for this review, the outcomes described in the ENDEAR study are relevant in addressing the major symptoms observed in patients most likely to develop SMA type I. One limitation of the motor functional outcomes using the HINE Section 2 and the CHOP INTEND scoring is their infrequent use in practice, as described by the clinical expert. Another limitation of the ENDEAR study is the inability of infants to self-report adverse events, such as headache, back pain, and dizziness. As such, these potentially common adverse events that are expected due to the lumbar puncture may not be given attention. In addition, no assessment of caregivers' quality of life or the burden of the disease was conducted in the study.

SMA is a lifelong disease that potentially may require nusinersen treatment for many years. The ENDEAR study provides evidence regarding the efficacy of nusinersen for up to 10 months of treatment and an additional 3 months of follow-up. Moreover, the trial was concluded early, [redacted] As such it is difficult to generalize the results of the ENDEAR study on to patients that have been diagnosed with infantile-onset SMA for a duration longer than 26 weeks.

Efficacy

Only those efficacy outcomes and subgroups identified in the review protocol are reported below (Section 2.2, Table 2). See Table 8 for summary of efficacy data.

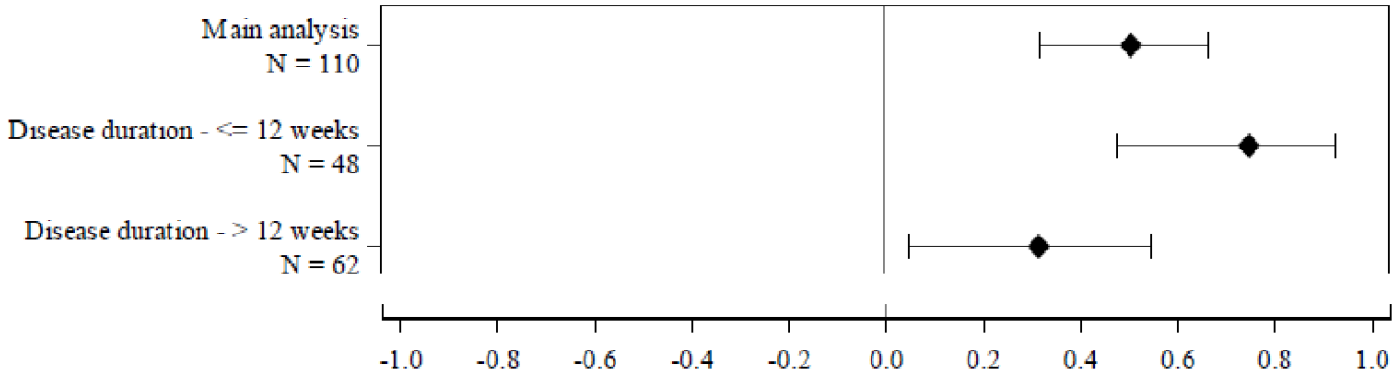
HINE Section 2 motor milestone responders

The first primary outcome, the proportion of motor milestone responders was analyzed based on the efficacy analysis set. In this set, 37 patients out of 73 in the nusinersen group (51%) compared with 0 patients out of 37 in the sham procedure control group were classified as responders. There was a statistically significant difference between groups in

the percentage of patients who were classified as motor milestone responders (50.7, 95% CI, 31.8 to 66.5, *P* < 0.0001). All conducted sensitivity analyses showed similar results to the base case. At the data cut-off date, 16 patients (22%) achieved full head control, 6 (8%) achieved independent sitting, and 1 (1%) achieved standing in the nusinersen group, whereas no patients in the sham procedure group achieved any of these milestones.

Subgroup analyses based on the median disease duration (less than and equal to12 weeks, greater than 12 weeks) were performed, however, results are considered exploratory as these analyses were outside of the stage-wise hierarchical strategy and, therefore, not adjusted for multiplicity.

Figure 2: Differences in the Proportion of Motor Milestone Responder Subgroups – Efficacy Set



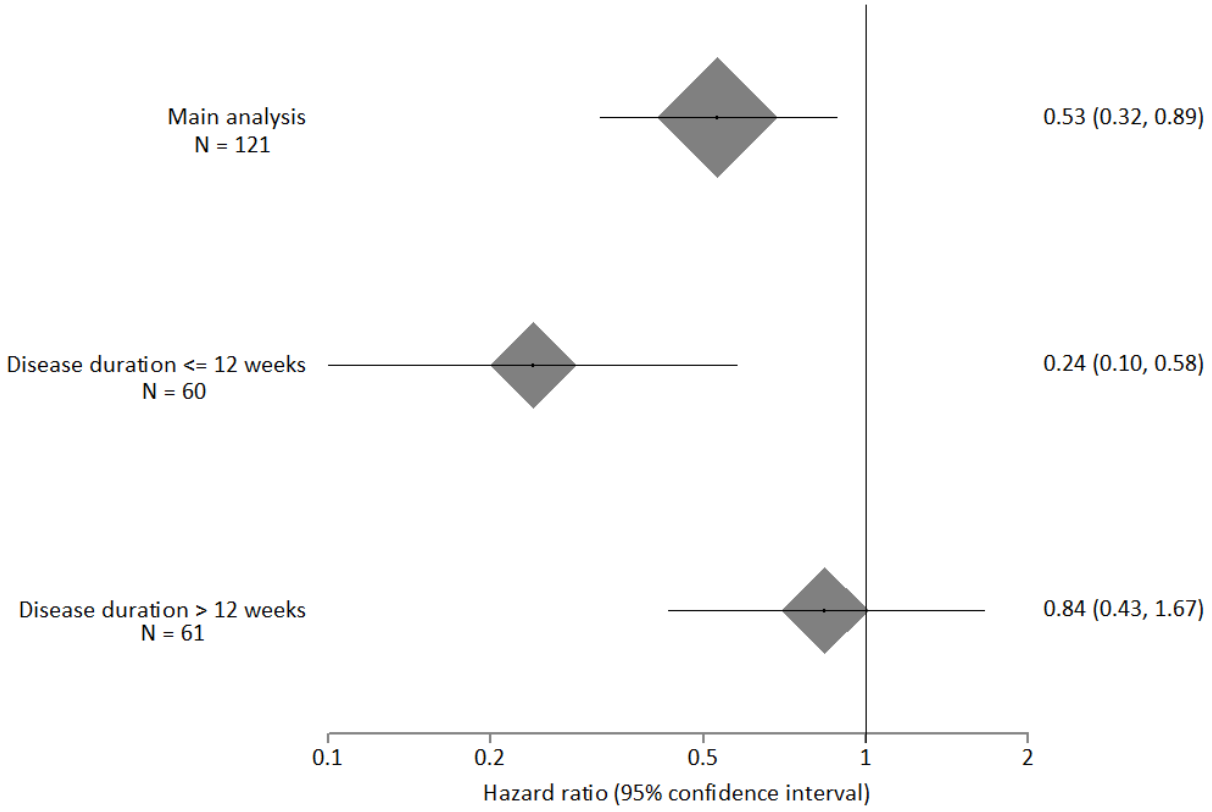
Source: Clinical study report: ISIS 396443-CS3B [17]

Time to death or permanent ventilation

The second primary outcome was analyzed using the ITT analysis set. Thirty-one patients (39%) in the nusinersen group died or required permanent ventilation versus 28 patients (68%) in the sham procedure group resulting in a statistically significant difference between groups (hazard ratio [HR] 0.53 [95% CI, 0.32 to 0.89], *P* = 0.0164). Seven sensitivity analyses were conducted in relation to event definition, statistical model, and analysis population (described in the statistics section). The results of the sensitivity analyses were similar to the primary analysis.

The results of the subgroup analysis based on median disease duration (less than and equal to 12 weeks, greater than 12 weeks), showed statistically significant differences compared with the sham procedure group in the subpopulation below the median disease duration (HR = 0.24, 95% CI, 0.10 to 0.58) but failed to show statistically significant differences in the subpopulation over the disease median duration (HR = 0.84, 95% CI, 0.43 to 1.67), Figure 3. However, due to the non-significance of a prior outcome in the stage-wise hierarchical strategy, (percentage of patients not requiring permanent ventilation) these analyses can only be considered exploratory and inconclusive.

Figure 3: Hazard Ratio of Event-Free Survival in Subgroup of Patients Below and Above the Median Disease Duration – ITT Set

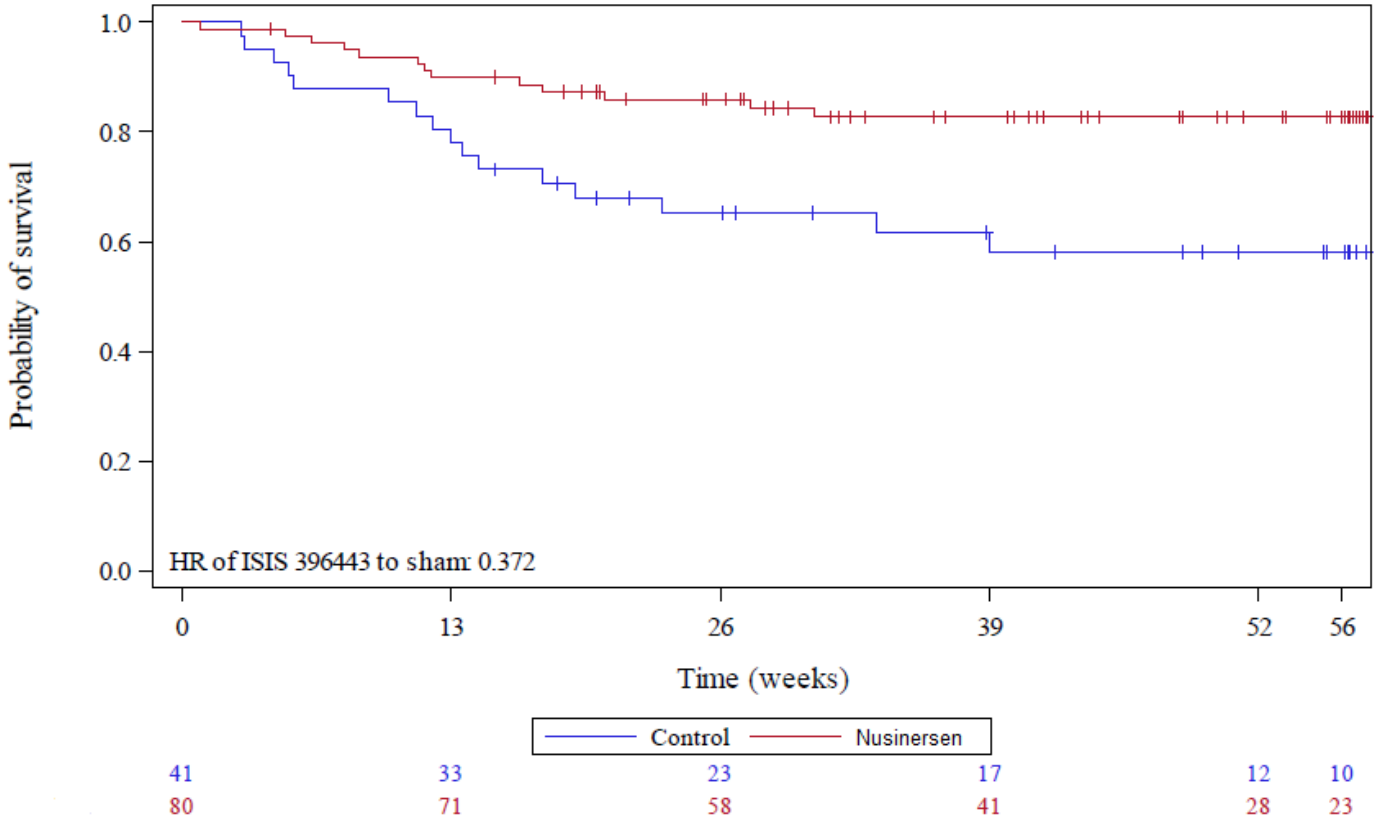


Source: Clinical study report: ISIS 396443-CS3B.[17]

Overall survival

When considering time to death in both groups, analysis using the ITT set indicated a statistically significant difference between nusinersen group and the sham procedure (HR = 0.37, 95% CI, 0.18 to 0.77). A Kaplan-Meier curve is presented in Figure 4.

Figure 4: Kaplan-Meier Curves for Time to Death – ITT Set



Source: Clinical study report: ISIS 396443-CS3B.[17]

Proportion of patients requiring permanent ventilation

When considering the proportion of patients requiring permanent ventilation in both groups, analysis using the ITT set did not show a statistically significant difference (HR = 0.66, 95% CI, 0.32 to 1.37). Because of the non-significance of this result, all subsequent tests in the statistical hierarchy were then considered exploratory.

CHOP INTEND improvement

Analyzed using the efficacy set, patients in the nusinersen experienced greater proportion of patients that were able to achieve an improvement of four or more points (71%) compared with patients allocated to the sham procedure group (3%).(percentage difference = 68.53, 95% CI, 51.27 to 81.99, *P* < 0.0001).

Growth parameters

This was an exploratory outcome, and as such any result is nominal and can only support hypothesis generation. [redacted]

[redacted]

Table 8: Key Efficacy Outcomes

	ENDEAR	
HINE Section 2 Motor Milestone Responders	**Nusinersen**	**Control**
Number of patients, N[a]	73	37
Motor milestone responders (improvement of any HINE categories in which there are more categories with improvement than with worsening), N (%)	37 (51)	0
Difference in percentages between treatment groups (95% CI)	50.7 (31.8, 66.5)	
P value	< 0.0001	
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
Walking: at least a 1-point increase	0 (0)	0
CHOP INTEND		
Number of patients, N[a]	73	37
Baseline CHOP INTEND score, mean (SD)	26.5 (8.2)	28.0 (7.6)
Change from baseline in total score improved ≥ 4 points, n (%)	52 (71)	1 (3)
[redacted]	[redacted]	
P value	< 0.0001	
Time to death or permanent ventilation		
Number of patients, N	80	41
Number of patients who died or required permanent ventilation, n (%)	31 (39)	28 (68)
Estimated proportion of patients who died or required permanent ventilation by:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Median survival time (wks), median (95% CI)	NA (36.3 to NA)	22.6 (13.6 to 31.3)
Hazard ratio (95% CI)	0.53 (0.32 to 0.89)	

	ENDEAR	
P value	0.0164	
Overall survival		
Number of patients, N	80	41
Number of patients who died	13 (16)	16 (39)
Estimated proportion of patients who died by:		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	0.37 (0.18 to 0.77)	
P value	0.0082	
Permanent ventilation		
Number of patients, N	80	41
Number of patients who required permanent ventilation	18 (23)	13 (32)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
Growth parameters		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
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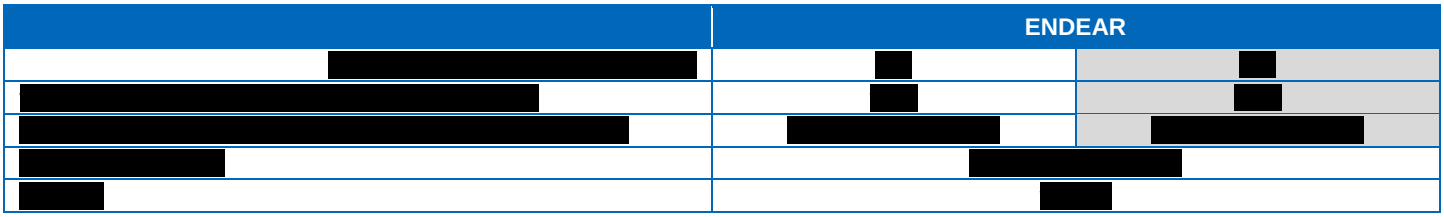

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; N = total number of patients; n = number of patients in subgroup; NA = not applicable; RULM = Revised Upper Limb Module; WHO = World Health Organization; wks = weeks.

[a] Efficacy Set: All patients with a recorded study visit on day 183, 302, or 394 and all patients with a time difference of at least 190 days between date of first dose and the cut-off date for the final analysis.

[b] Adjusted for age at symptom onset and disease duration at screening.

Source: Clinical study report: ISIS 396443-CS3B.[17]

Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). Summary of harms is presented in Table 9.

Adverse events

At least one adverse event was reported in 96% of all enrolled patients. None of the adverse events were considered related to the study treatment by the study investigators. The only lumbar puncture-related adverse event reported was vomiting, which was observed in 5% in the nusinersen group but not in the control group. Withdrawals due to adverse events (WDAE) were due to fatal adverse events only, an outcome captured by the second primary outcome of the study.

Serious adverse events

A lower percentage of patients in the nusinersen group had a serious adverse event (SAE) compared with the sham control group (nusinersen vs. control: 76% vs. 95%).

Withdrawals due to adverse events

All WDAE were due to the death of the patient. There were numerically higher WDAE in the control group (39%) versus the nusinersen group (16%).

Mortality

There were 16 deaths (39%) reported in the control group versus 13 deaths reported in the nusinersen group (16%). Deaths were attributed to respiratory, thoracic, and mediastinal disorders were the highest proportion in both groups (9% in the nusinersen group and 29% in the control group).

Notable harms

Vomiting was noted in the nusinersen group as related to the lumbar puncture procedure (5% in nusinersen group, 0% in the control group). Two patients (3%) in the nusinersen treatment arm were reported as having an adverse effect related to renal and urinary disorders, compared with one patient (2%) in the control group.

Table 9: Harms

	ENDEAR	
AEs	**Nusinersen N = 80**	**Control N = 41**
Patients with > 0 AEs, N (%)	77 (96)	40 (98)
Infections and infestations	65 (81)	31 (76)
Respiratory, thoracic, and mediastinal disorders	61(76)	36 (88)
Gastrointestinal disorders	53 (66)	26 (63)
General disorders and administration site conditions	51 (64)	28 (68)
Skin and subcutaneous tissue disorders	23 (29)	15 (37)
Investigations	21 (26)	14 (34)
Cardiac disorders	19 (23)	13 (32)
Injury, poisoning, and procedural complications	19 (24)	10 (24)
Metabolism and nutrition disorders	14 (18)	13 (32)
Musculoskeletal and connective tissue disorders	11(14)	5 (12)
Psychiatric disorders	9 (11)	5 (12)
Nervous system disorders	9 (11)	2 (5)
Congenital, familial, and genetic disorders	4 (5)	4 (10)
Blood and lymphatic disorders	1 (1)	3 (7)
SAEs		
Patients with > 0 SAEs, N (%)	61 (76)	39 (95)
Respiratory distress	21 (26)	8 (20)
Respiratory failure	20 (25)	16 (39)
Pneumonia	19 (24)	5 (12)
Atelectasis	14 (18)	4 (10)
Acute respiratory failure	11 (14)	9 (22)
Pneumonia aspiration	8 (10)	5 (12)
Rhinovirus infection	7 (9)	2 (5)
Respiratory tract infection	6 (8)	1 (2)
Cardiorespiratory arrest	5 (6)	5 (12)
Respiratory arrest	5 (6)	4 (10)
Viral infection	5 (6)	1 (2)
WDAEs		
WDAEs, N (%)[a]	13 (16)	16 (39)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	ENDEAR	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Deaths		
Number of deaths, N (%)	13 (16)	16 (39)

AE = adverse event; N = total number of patients; SAE = serious adverse event; WDAE = withdrawals due to adverse events.

[a] All WDAE were caused by the death of the patient.

Source: Clinical study report: ISIS 396443-CS3B. A phase III, randomized, double-blind, sham-controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with infantile-onset spinal muscular atrophy [**CONFIDENTIAL** internal manufacturer's report].[17]

Discussion

Summary of Available Evidence

One randomized, double-blind, sham-controlled, phase III clinical trial was included in this review: the ENDEAR study. The study recruited patients up to 7 months of age with infantile-onset SMA with documented 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote, and only two copies of the SMN2 gene. These characteristics make this group of patients likely to develop SMA type I. In addition, the resulting baseline characters of enrolled patients indicate that all of them were relatively recently diagnosed with SMA (between 0 weeks and 25.86 weeks of disease duration).

Additional studies assessing the safety and efficacy of nusinersen that did not meet the inclusion criteria due to study design and/or intervention include two single phase II single-arm trials (non-matching dosing, as well as CS3A not matching the dosing regimen of the nusinersen) and one phase III randomized controlled trial (not matching the dosing regimen of nusinersen), which were summarized in Appendix 4.These studies assessed the efficacy and safety of nusinersen in presymptomatic patients (NURTURE study), infantile-onset SMA (CS3A), and childhood-onset SMA (CHERISH). In addition, extension and long-term safety studies assessing the safety of nusinersen were also summarized in Appendix 6.

Interpretation of Results

Efficacy

The ENDEAR study randomized 121 patients with SMA (likely to develop SMA type I) in a 2:1 ratio to nusinersen treatment and sham procedure control group, respectively. There were two primary outcomes: motor milestone responders according to the HINE Section 2 tool, and time to death or permanent ventilation. After the interim analysis of the first primary outcome, HINE Section 2 motor milestone responders, the positive results led to the premature termination of the study to allow patients in the sham procedure group the opportunity to receive the nusinersen treatment. The final analysis demonstrated a statistically significant difference in the proportion of HINE 2 motor milestone responders between the nusinersen treatment group and the sham procedure control group (difference in percentage = 50.7, 95% CI, 31.8 to 66.5). Several sensitivity analyses using different definitions of responders and different analysis sets supported the primary analysis. When analyzing this outcome in subgroups of patients that had disease duration of 12 weeks or of less and patients with disease duration of more than 12 weeks, a statistically significant difference was maintained. However, it should be noted that this was an exploratory analysis, not adjusted for multiplicity. The captured improvements in motor milestones of patients was also supported by a second motor milestone measure, the CHOP INTEND, where 71% of the patients allocated to nusinersen treatment achieved an improvement of 4 or more points on the CHOP INTEND scale as compared with 3% in the sham procedure control group (percentage difference = 68.53, 95% CI, 51.27 to 81.99). Regarding the validity of the motor milestone tools used in the ENDEAR study, the HINE Section 2: Motor Milestones has adequate test-retest reliability.[24] Change in the score moderately correlates with change in other measures of motor function in type I SMA patients receiving nusinersen.[24] The definition of treatment responders have been noted in Health Canada Reviewer Report to be broad in that it captures many patients with minimal improvement,

and treats those patients in a similar way to those that gained more significant improvements.[20] Natural history in type I SMA patients suggests that an improvement greater than one point in any milestone is highly unlikely.[19] The CHOP INTEND is a set of activities assessing motor function in infants and children with neuromuscular disorders.[21] It has adequate intra-rater and inter-rater reliability,[25] and its construct validity has been demonstrated in patients with type I SMA.[26,27]

The second primary outcome in the ENDEAR study, time to death or permanent ventilation, is more difficult to interpret. The main analysis indicated that 31 patients (39%) in the nusinersen group died or required permanent ventilation versus 28 patients (68%) in the sham procedure group during a period of roughly approximately 13 months (Hazard ratio = 0.53, 95% CI 0.32 to 0.89). However, when the manufacturer conducted a subgroup analysis based on the median disease duration (less than and equal to 12 weeks, greater than 12 weeks), the results showed statistically significant differences compared with the sham procedure group in the subgroup below the median disease duration (HR = 0.24, 95% CI, 0.10 to 0.58) but failed to show statistically significant differences in the subpopulation over the disease median duration (HR = 0.84, 95% CI, 0.43 to 1.67). Moreover, when broken down to each event type separately, the results indicated a statistically significant difference between nusinersen group and the sham procedure in overall survival (HR = 0.37, 95% CI, 0.18 to 0.77), but not in time until permanent ventilation (HR = 0.66, 95% CI, 0.32 to 1.37). It is possible, however, that due to the loss of data from the premature termination of the study, as well as the shortened duration of follow-up, statistical power was reduced. [redacted]

The early termination of the ENDEAR study caused data loss as well as reduction in the time of assessing the efficacy and safety of nusinersen. These two factors may have also contributed to a lack of statistical power necessary to capture differences in the secondary and subgroup outcomes that showed no statistically significant differences. However, it is unlikely that this limitation has affected the two primary outcomes. Health Canada, the European Medicines Agency, and the FDA have all reviewed ENDEAR trial and did not report any major concerns regarding the internal validity of the study.[20,23,28]

The limitation to the external validity of the study mainly revolved around the inability to generalize the results to patients with infantile SMA who had a disease duration of more than 30 weeks, or who have three copies of the SMN 2 gene, as those population are not represented in the study. This becomes important when considering that the natural disease progression of patients who are likely to be in the SMA type I subtype is characterized by a rapid onset of irreversible motor neuron degeneration,[3] and that the mechanism of action of nusinersen requires viable motor neuron to work on, it can be seen that generalizing the results to patients with a disease duration longer than the patients enrolled in ENDEAR can be extremely uncertain. Although the CS3A phase II single-arm trial has attempted to include patients with the phenotype of SMA type I regardless of the

SMN2 gene copy number, the design of the study, as a phase II single-arm descriptive trial, and the different regimen of the intervention makes the results ungeneralizable.

Efficacy results from other supportive evidence is also limited in generalizability due to either study design (NURTURE was a single-arm, non-comparative, descriptive, phase II), or different treatment regimen (CHERISH did not provide the Health Canada indicated treatment regimen). However, in NURTURE, presymptomatic infantile SMA patients who undertook nusinersen treatment showed no fatalities after six months of assessment, while in the CHERISH trial, nusinersen-treated patients with childhood-onset SMA exhibited a statistically significant gain in motor function compared with patients in the sham control group.

Harms

Throughout all the manufacturer-provided trials, the most common adverse events are related to infections and/or respiratory problems, two common complications of SMA. A number of patients (5%) in the nusinersen treatment arm experienced vomiting which was related to the lumbar puncture procedure. A lower percentage of percentage reported SAEs in the nusinersen arm (76%) than in the sham procedure arm (95%). Extension and long-term safety studies reported a similar safety profile. The Health Canada product monograph suggests that the majority of the reported adverse events are related to the disease process or the lumbar puncture procedure.[6]

Limitations of the safety results in the ENDEAR study included the inability of patients to report adverse events that do not show clinical signs. These include adverse events that may be related to the lumbar puncture procedure (e.g., headache, backache). In addition, there is lack of long-term safety data, which is important to note considering the lifelong nature of the disease.

Potential Place in Therapy[2]

SMA results in the irreversible loss of motor neurons and motor nerves. The loss of these nerves causes skeletal muscles to become progressively weaker giving rise to swallowing problems and breathing difficulties and/or weakness of the limbs and trunk. A natural history study using a specialized neurophysiological technique called motor unit number estimation (MUNE) has found that there is a relatively rapid loss of motor neurons early in the course of the disease followed by a more gradual decline.[3] As such, the optimal time for intervention is early in the course of the disease before this rapid andirreversible loss of motor neurons has occurred.

SMA is diagnosed in Canada via genetic testing. Initial testing evaluates for the homozygous 5q deletion within the survival motor neuron 1 gene (SMN1) which identifies 95% of cases. If negative, SMN1 gene sequencing will be performed as a second step. Nerve conduction studies and electromyography (EMG) is performed in a subset of patients, however even when evidence of a motor neuronopathy is identified on this study it is followed up with confirmatory genetic testing.

Current standard of care practice for patients with confirmed SMA include surveillance and anticipatory management ensuring that patients receive monitoring of: 1) growth, gastrointestinal function and nutrition; 2) respiratory complications and; 3) orthopedic complications (i.e., scoliosis and/or contractures).[4] Anticipatory management of respiratory

2 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

complications are particularly important for children with SMA type I and II since these patients are at high risk of having a weak cough with impaired clearance of airway secretions; nocturnal hypoventilation and; recurrent pulmonary infections. This standard of care is not expected to change with emerging therapies, however it is hoped that the progression and complications of this disease may be lessened.

Nusinersen is the only Health Canada–approved treatment that is available for children with SMA. Treatment is administered via intrathecal injection and has been shown to be safe in several clinical trials.[5,6] There is convincing evidence that nusinersen is effective for children with SMA type I. This includes both early, asymptomatic infants with SMA type I (NURTURE study) and young (less than 7 months old) symptomatic infants with SMA type I (ENDEAR study).[5,6] Treated infants show improved survival (compared with natural history data) as well as improvement in their gross motor development as measured by the HINE. Clinical improvement was even more pronounced when infants were treated earlier, particularly when presymptomatic.[5] According to the clinical expert consulted for this review, given these results, nusinersen should be available for all Canadian infants with SMA type I. Knowing that presymptomatic treatment with nusinersen offers the greatest potential for preventing irreversible loss of motor neurons, physicians and public health agencies must consider what can be done to ensure early diagnosis including the potential for including SMA into provincial newborn screening programs.

Nusinersen has also demonstrated efficacy for children (aged 2 to 12 years old) with SMA type II (CHERISH study). The interim results of a placebo-controlled trial identified children to show an improvement in motor strength and function as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). Since children's muscle fibres undergo an increase in size over the first few years of life, a process known as physiological hypertrophy, any intervention to prevent the irreversible loss of motor neurons and consequently, allow muscle fibres the potential to more normal development is advantageous. Early recognition and treatment is also important in this group. Although nusinersen has not been well studied in children with SMA type III, it would be predicted that children in this group would have a greater potential for increasing SMN protein, if treated early in the course of their disease. Patients with SMA type III comprise about 10-20% all patients with SMA2. These children have had the ability to walk at some point although this can be lost as the disease progresses. Early treatment of patients with SMA type III, particularly young patients with apparent rapid disease progression would have the theoretical potential of preventing loss of ambulation with the significant gain of independence and avoidance of numerous medical complications that can result in non-ambulatory patients.

Conclusions

One randomized, double-blind, sham-controlled trial (ENDEAR, N = 121) met the inclusion criteria of the CDR systematic review. Patients included in the ENDEAR trial had a confirmed diagnosis of SMA, were less than seven months or age, had only two copies of the SMN2 gene, had a disease duration of no more than 25.86 weeks, and were most likely to develop SMA type I. Patients were randomized in a 2:1 ratio to nusinersen treatment or a sham control group. Patients were to receive ten months of treatment and have an additional three months of follow-up, however, the ENDEAR trial was concluded early based on positive results from a pre-planned interim analysis. There were statistically significant differences between the two groups, in favour of the nusinersen group, for both

co-primary end points in the ENDEAR trial: the proportion of motor milestone responders as assessed by the HINE Section 2 tool and the time to death or permanent ventilation. No adverse events in the ENDEAR trial were considered by the study investigators to be related to the study treatment. The percentage of patients experiencing a SAEs and WDAEs were lower in the nusinersen treatment group versus the sham procedure arm. The main limitations of the ENDEAR trial was the early termination of the study which caused loss of data and a shorter time period to assess the efficacy and safety of nusinersen, and the inability to generalize the results to patients with infantile-onset SMA who had disease durations of more than 26 weeks.

Supportive evidence from two phase II trials (NURTURE, CS3A), one phase III trial (CHERISH), and two extension and long-term safety studies provided additional safety and efficacy data for patients who are likely to develop SMA type I and II. Presymptomatic patients who received nusinersen treatment in the NURTURE trial showed no fatalities after six months of assessment, while in the CHERISH trial, nusinersen-treated patients with childhood-onset SMA experienced a statistically significant gain in motor function compared with patients in the sham control group. No new safety signals were identified in any of the supporting studies. These studies, however, were limited due to study design (single-arm, non-comparative, descriptive, or phase II), and/or the use of a treatment regimen or dose that was not approved by Health Canada.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

One submission was prepared jointly by the Canadian Organization for Rare Disorders (CORD) and Cure SMA Canada, both registered charities. CORD advocates on behalf of those with rare disorders and provides support to patient groups. Cure SMA Canada provides support to those affected by spinal muscular atrophy (SMA), resources to families, communities, and health professionals, and funding for research. A second submission was prepared by Muscular Dystrophy Canada (MDC), a national, non-profit organization which provides support to Canadians affected by neuromuscular disorders in navigating systems, accessing resources, and providing information and education. Both CORD and MDC have received $5,001 to $10,000 in funding from Biogen, the manufacturer of Spinraza, within the past two years. No other conflicts of interest were declared.

2. Condition-Related Information

The joint submission of CORD and Cure SMA Canada was based on the results of one focus group, four interviews, and a survey. Most of the respondents were caregivers and family members. MDC interviewed caregivers and patients for their submission. The remainder of this appendix is based on information gathered through these sources.

SMA affects patients with widely ranging degrees of severity depending on age of onset. SMA type I presents by the age of six months and is the most common genetic cause of infant mortality. In SMA type II, age of onset is six to 18 months and patients have delayed motor milestones, respiratory issues, and possibly shortened life expectancy. SMA type III patients are those with onset from 18 months to 18 years of age and they experience muscle weakness. SMA type IV is adult-onset with varying degrees of muscle weakness. Common to all types of SMA is a progressive decline in muscle function.

Reactions to receiving an SMA diagnosis are overwhelmingly negative, with feelings of despair and frustration over the lack of effective treatments for SMA. One parent described difficulty in obtaining an accurate diagnosis for their two-month-old daughter who “was turning blue and had breathing issues.” The survey found significant proportions of respondents with major problems or inability in each of the following areas: walking, muscle strength (lack of weakness, pain, or fatigue), fine motor skills, (deep) breathing, and swallowing or feeding. Inability to walk means relying on wheelchairs and other mobility aids and dealing with associated barriers. Assistance may be required to transfer to and from mobility aids. Those who can walk with assistance may not be able to get up, use the stairs, bathe, or use the toilet independently. Young patients also miss out on typical childhood experiences such as using the playground. In more severe cases, patients cannot execute basic movements such as sitting up and require help with needs such as transfers as well as positioning in wheelchair and in bed. One parent of a type II patient noted their daughter “cannot do anything independently. If she has an itch in the middle of the night, she can’t even scratch it.” Of their infant daughter with type I SMA, one parent said, “She could only slightly wiggle or move her hands; she even lost the ability to smile or frown.” Loss of independence and reliance on assistance for daily care tasks leads to extra time and difficulty in navigating situations that would be normal for others. Difficulty in swallowing may necessitate use of a feeding tube and difficulty in breathing maybe lead to

reliance on mechanical ventilation during nights or around the clock. The parent of a young type III patient stated, “She has difficulty breathing at night and suffers from severe sleep apnea. Her tonsils and adenoids were removed to buy some more time but she will soon need a machine to help her breathe at night.” For young adults, all of these difficulties present barriers to moving away from home, finding work, and making friends. There is also awareness of the burden placed on family members.

Progressive, life-changing loss of motor function and abilities has devastating effects, with changes such as “walking to standing to power chair in 5 years” and losing the ability to perform daily hygiene tasks or even breathe and swallow independently. There is great frustration over this progressive decline for adults and children alike, with one patient calling it “the hardest part.” One parent recounted how her daughter “fell and cried and with tears in her eyes she said, ‘mommy I’m broken’.” One young adult confined to a wheelchair expressed expectations of further decline and not being able to achieve milestones in the future such as home ownership or having children.

The lives of families and caregivers of SMA patients are profoundly affected, with one parent stating, “We live and breathe SMA daily.” A lot of time and physical support goes into caring for an SMA patient and often a family member has to reduce or leave employment to accommodate appointments and provide constant monitoring and assistance. One respondent described a “constant crisis mode.” Physical care can be complex and tough on the body (e.g., transfers). Patients are vulnerable to illness, leading to difficulty and anxiety associated with going out in public, attending social functions, and travelling, all of which have an isolating effect on families (“it’s hard to get out of the house, hard to enjoy life”). The progression in paralysis and loss of function has a psychological and emotional impact on families, with one parent describing it as “frustrating and heartbreaking to witness.” Caregivers struggle with fear of the unknown and burnout. There is also the financial burden of out of pocket costs (“each year we have spent $18,000-$20,000 out of pocket for expenses which are not covered”) as well as difficulties in securing insurance coverage and government funding. Families are the main caregivers out of necessity because outside resources are lacking.

3. Current Therapy-Related Information

Treatments for SMA include mobility aids, breathing support, spinal treatment, feeding tube, physiotherapy, speech therapy, and medications. Survey respondents indicated a wide range of effectiveness of mechanical aids and physiotherapy in managing SMA symptoms, from performing “very well” to not being effective. Some parents noted that assistive devices provide quality of life improvements such as increased mobility, better sleep, weight gain, strength, and posture. One parent noted initial resistance of their child to bi-level positive airway pressure (BiPAP) therapy. Despite the improvements to quality of life, patients and caregivers are well aware that current care only helps with symptoms and does not treat SMA itself or stop its progression.

Parents of infants with type I SMA would like to see treatment that improves breathing as well as ability to feed and perform small movements like rolling over. Parents in general would like a treatment that reduces pain, controls loss of mobility, improves muscle function and allows their children to continue performing activities such as daily self-care (feeding, operating a wheelchair, writing) independently for as long as possible. Patients themselves place importance on slowing disease progression and maintaining independence which would allow them to continue with school or work.

4. Expectations About the Drug Being Reviewed

There is hope that Spinraza will improve overall quality of life, maintain or restore respiratory function and muscle strength and movement, slow or stop disease progression, and lessen dependence on others. The newly diagnosed hope it will prevent symptoms from manifesting. Interview subjects felt that Spinraza could prevent the irreversible loss of motor neurons, reducing the risk of losing mobility and ability to perform self-care tasks and the risk of requiring respiratory support.

Most parents of patients who have received Spinraza are enthusiastic and optimistic about the experience, reporting improvements in physical capabilities. One parent described the treatment as a “miracle”. The improvements include: stronger breathing, speech, and coughing; increased physical strength, energy, movement, and eating; joints no longer contracting; ability to perform new actions such holding one’s head up, rolling over, bearing weight on legs, raising arms and legs to and above the head, sitting or standing up with and without assistance, and using mobility aids. One parent who has seen many of these improvements in their daughter stated, “She is a much happier baby and is able to explore and play. We have not had increased medical need for her since we began. It has given her so much more independence.” Improvements can also lead to increased mobility in older children, for example: “He is now able to stand assisted (and briefly unassisted) with AFOs [ankle-foot orthoses] and we are working on getting him comfortable and strong enough to be able to use crutches or a walker.” Parents also described faster and more complete recovery from illness leading to less anxiety. One parent who dealt with recent bouts of illness said, “[…] afterwards his strength came back as well as a little bit more. This would be unheard of [when] he wasn’t on Spinraza!” There have also been positive effects on mood and confidence in patients. The effects described above have resulted in increased optimism of families for the future.

Most parents indicated very few side effects, if any, related to the drug or its administration. The most common side effects were constipation and headache. Once problems associated with injections were solved (e.g., fasting, lack of sedation), subsequent injections went well. Side effects and anxiety were mentioned with lumbar puncture but were considered manageable. Challenges associated with treatment include obtaining access, travelling with a patient with complex care needs, and the time off work and costs associated with travelling.

Given the progressive nature of SMA and the potential of Spinraza to treat the disease itself, the drug is considered to be very important for patients of all SMA types. There is a strong sense of urgency to make the drug available to all SMA patients, regardless of type, to prevent death and loss of function.

4. Additional Information

Common concerns expressed with current access to Spinraza include: affordability, restriction of availability to SMA type I, difficulty in travel, difficulty in navigating the process, and access in rural areas.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 27 2017
Alerts:	Bi-weekly search updates
Study Types:	No search filters were applied
Limits:	No date or language limits were used

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search**
1	(Spinraza* or Nusinersen* or 5Z9SP3X666 or ISIS 396443 or ISIS396443 or ISIS-SMNRx or ISISSMNRx or ASO-10-27).ti,ab,kf,ot,hw,rn,nm.
2	(1258984-36-9 or "1258984369" or 5Z9SP3X666).rn,nm.
3	1 or 2
4	3 use ppez
5	*nusinersen/
6	(Spinraza* or Nusinersen* or 5Z9SP3X666 or ISIS 396443 or ISIS396443 or ISIS-SMNRx or ISISSMNRx or 1258984-36-9 or "1258984369" or 5Z9SP3X666 or ASO-10-27).ti,ab,kw.
7	5 or 6
8	7 use oemezd
9	4 or 8

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	July 2017
Keywords:	Spinraza, Nusinersen
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Finkel, 2016[29]	Study design
Clinical study report: ISIS 396443-CS3A, 2016[30]	Duplicate/ study design
Clinical study report: ISIS 396443-CS4 (CHERISH), 2017[31]	Intervention
Progress report: 232SM202	Study design
NURTURE (SM201) [32]	Study design
Progress report: ISIS 396443-CS11 [33]	Study design

Appendix 4: Summary of Other Efficacy Studies

Introduction

The manufacturer of nusinersen has conducted trials that included various subpopulations of patients diagnosed with SMA. These trials did meet the inclusion criteria set out for this review. Phase I studies were used to inform the economic analysis. These studies included CS2 and CS12. CS2 was a phase I, open-label, dose-escalation study aimed to assess findings from multiple nusinersen doses, none of which matched the Health Canada–approved dose. The primary focus of CS2 was on pharmacodynamics and pharmacokinetics related outcomes. CS12 was an open-label, single-arm, extension study of patients that completed one of two phase I trials (CS1 or CS10). The primary aim of CS12 was to report on tolerability and clinical laboratory parameter changes during the study conduct.

Aim

To provide a summary of additional studies assessing clinical information on potential efficacy and safety of nusinersen in phase II and phase III trials that did not meet the inclusion criteria for the CADTH Common Drug Review (CDR) systematic review. Phase I trials were not considered, as limited information on efficacy can be obtained from these studies due to the nature of the design.

Included Studies

Table 10: Details of Included Studies

		NURTURE (CS5)	CHERISH (CS4)	CS3A
Designs & Populations	**Study Design**	Phase II, multi-centre, open-label, uncontrolled single-arm trial	Phase III, randomized, double-blind, sham-controlled, multi-centre trial	Phase II, open-label, multiple dose, multi-centre trial
	Locations	Australia, Argentina, Germany, Israel, Italy, Qatar, Taiwan, Turkey, the UK, and the US	North America (Canada and US), Europe, Asia-Pacific region	Canada, US
	Enrolled (N)	25 (planned)	126	20 (planned)
	Inclusion Criteria	• Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation • Genetic documentation of 2 or 3 copies of SMN2 • Age ≤ 6 weeks at first dose. • Ulnar CMAP ≥ 1 mV at baseline	• Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote • Onset of clinical signs and symptoms consistent with SMA at > 6 months of age • Males and females 2 to 12 years of age • Could sit independently, but has never had the ability to walk independently • Motor Function Score (HFMSE) ≥ 10 and ≤ 54 at screening	• Genetic documentation of 5q SMA homozygous gene deletion or mutation • Onset of clinical signs and symptoms consistent with SMA at ≥ 21 days and ≤ 6 months (180 days) of age • Males and females between ≥ 21 days and ≤ 7 months (210 days) of age at screening
	Exclusion Criteria	• Hypoxemia • Signs or symptoms at Screening or immediately prior to the first dosing (day 1) that	• Respiratory insufficiency • Gastric feeding tube • History of or active condition that would interfere with lumbar	• Hypoxemia • History of or active condition that would interfere with lumbar puncture or

		NURTURE (CS5)	CHERISH (CS4)	CS3A
		are strongly suggestive of SMA • History of or active condition that would interfere with lumbar puncture or assessment of study • Treatment with an investigational drug given for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea, etc.), biological agent, or device • Any history of gene therapy, prior ASO treatment, or cell transplantation	puncture or assessment of study • Treatment with another investigational drug (e.g., oral albuterol/salbutamol, riluzole, carnitine, creatine, sodium phenylbutyrate, etc.), biological agent, or device within 1 month of screening or 5 half-lives of study drug, whichever was longer • Treatment with valproate or hydroxyurea within 3 months of screening • Any history of gene therapy, ASO therapy, or cell transplantation	assessment of study • Treatment with another investigational drug (e.g., albuterol, riluzole, carnitine, creatine, sodium phenylbutyrate, salbutamol, valproate, hydroxyurea), biological agent, or device within 90 days prior to enrolment or anytime during the study • Any history of gene therapy or cell transplantation
Drugs	**Intervention**	12 mg (in a 5 mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen administered intrathecal by lumbar puncture on days 1, 15, 29, 64, 183, 302, 421, 540, 659, and 778 of the study	12 mg (in a 5 mL solution) nusinersen administered intrathecal by lumbar puncture days 1, 29, 85, and 274	Cohort 1: 6 mg (in a 5 mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen on days 1, 15, 85 Cohort 2: 12 mg (in a 5-mL solution) scaled equivalent dose based on CSF volume scaling of nusinersen on days 1, 15, 85 Subsequently, both cohorts receive 12 mg equivalent on days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261
	Comparator(s)	NA	Sham procedure on days 1, 29, 85, and 274	NA
Duration	**Phase**			
	Screening	21 days	28 days	21 days
	Double-blind	NA (treatment period until day 778, or 111 weeks)	9 months	NA (treatment period until day 1261)
	Follow-up	3 months	6 months	3 months
Outcomes	**Primary End Point**	• Time to death or respiratory intervention (invasive or non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 days OR tracheostomy)	• Change from baseline in HFMSE score at 15 months	HINE Section 2 score
	Other End Points	• Respiratory events • Growth parameters • CHOP INTEND • WHO Motor Milestones • HINE Section 2	• Proportion of HFMSE responders • RULM • WHO Motor Milestones • PedsQL • ACEND • Hospitalization	• Event-free survival and survival • CHOP INTEND • Ventilator use • Growth parameters

		NURTURE (CS5)	CHERISH (CS4)	CS3A
Notes	**Publications**	"None"	"None"	Finkel 2016[29]

ACEND = Assessment of Caregiver Experience With Neuromuscular Disease; ASO = antisense oligonucleotide; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; mg = milligrams; mL = millilitres; mV = millivolts; N = total number of patients; NA = not applicable; PedsQL = Pediatric Quality of Life Inventory; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN = survival motor neuron; WHO = World Health Organization.
Source: Clinical study report: ISIS 396443-CS4, Progress report: 232SM202, and Clinical study report: ISIS 396443-CS3A.[30-32]

Summary of studies

Table 11: Summary of Baseline Characteristics

	NURTURE	CHERISH		CS3A
	Nusinersen (N = 20)	**Nusinersen (N = 84)**	**Control (N = 42)**	**Nusinersen (Cohort 2 N = 16)[a]**
Demographics				
Age at screening, mean (SD)	NR	3.8 (1.6) yrs	3.8 (1.6) yrs	140 (60) days
Age at first dose , mean (SD)	20.5 (11.41) days	NR	NR	NR
Female, n (%)	9 (45)	46 (55)	21 (50)	7 (44)
White, n (%)	10 (50)	30 (71)	64 (76)	13 (81)
Asian, n (%)	1 (5)	16 (19)	7 (17)	1 (6.3)
Weight kg, median (range)	3.5 (2.7 to 4.8)	14.0 (8.5 to 36.4)	13.2 (9.8 to 25.1)	6.6 (5.1 to 9.3)
SMN2 copy number				
Two copies, n (%)	13 (65)	6 (7)	4 (10)	13 (81)
Three copies, n (%)	7 (35)	74 (88)	37 (88)	2 (13)
Four copies, n (%)	0	2 (2)	1 (2)	0
Unknown, n (%)	0	2 (2)	0	1 (6)
Disease history				
Time from diagnosis to enrolment, mean (SD)	Presymptomatic	31.1 (20.05) mos	27.8 (18.5) mos	61 (38) days
Time from disease onset to enrolment, mean (SD)	Presymptomatic	39.9 (20.2) mos	34.8 (18.7) mos	77 (38) days
Age at symptom onset, mean (SD)	Presymptomatic	11.1 (3.3) mos	11.3 (3.4) mos	63 (42) days
Age at diagnosis, mean (SD)	Presymptomatic	19.9 (7.9) mos	18.3 (7.6) mos	80 (49) days
Disease symptoms				
Hypotonia, n (%)	Presymptomatic	NR	NR	15 (94)
Developmental motor delay, n (%)	Presymptomatic	NR	NR	14 (88)
Paradoxical breathing, n (%)	Presymptomatic	NR	NR	NR
Pneumonia or respiratory symptoms, n (%)	Presymptomatic	NR	NR	6 (38)
Limb weakness, n (%)	Presymptomatic	NR	NR	15 (94)
Swallowing or feeding difficulties, n (%)	Presymptomatic	NR	NR	6 (38)
HINE Section 2 characteristics				
Voluntary grasp: uses whole hand to grasp, n (%)	11 out of 19 (58)	NR	NR	13 (81)
Ability to kick: unable to kick, n (%)	2 (10)	NR	NR	5 (31)
Head control: unable to maintain head	10 (50)	NR	NR	13 (81)

	NURTURE	CHERISH		CS3A
	Nusinersen (N = 20)	**Nusinersen (N = 84)**	**Control (N = 42)**	**Nusinersen (Cohort 2 N = 16)[a]**
upright, n (%)				
Sitting: unable to sit, n (%)	20 (100)	NR	NR	15 (94)
Rolling: no rolling, n (%)	20 (100)	NR	NR	15 (94)
Crawling: does not lift head, n (%)	19 (95)	NR	NR	14 (88)
Standing: does not support weight, n (%)	15 (75)	NR	NR	15 (94)
Walking: no walking, n (%)	20 (100)	NR	NR	15 (94)
Motor milestones achieved				
Sat without support, n (%)	0 out of 14	84 (100)	42 (100)	NR
Stood without support, n (%)	0	11 (13)	12 (29)	NR
Walked with support, n (%)	NR	20 (24)	14 (33)	NR
Walked ≥ 15 ft independently, n (%)	NR	0	0	NR
Disease supports				
Used a wheelchair, n (%)	NR	64 (76)	29 (69)	NR
Attended physical therapy, n (%)	NR	78 (93)	38 (90)	NR

CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ft = feet; HINE = Hammersmith Infant Neurological Exam; kg = kilograms; mos = months; N = total number of patients; n = number of patients in subgroup; NR = not reported; SD = standard deviation; SMN2 = survival motor neuron 2; yrs = years.

[a] Cohort 2 received 12 mg of nusinersen as opposed to 66 mg in cohort 1; as such, the emphasis is on cohort 2.

Source: Clinical study report: ISIS 396443-CS4, Progress report: 232SM202, and Clinical study report: ISIS 396443-CS3A.[30-32]

Two phase II trials and one phase III trial are summarized in this appendix. NURTURE was a phase II, single-arm trial for patients with presymptomatic spinal muscular atrophy (SMA) who possessed two or three copies of the survival motor neuron (SMN)2 gene. CS3A was a phase II, single-arm trial in patients with symptoms suggestive of SMA type I, and CHERISH was a phase III randomized, sham-controlled trial for patients with symptoms suggestive of SMA type II. Patients were treated with nusinersen according to the Health Canada–approved product monograph in the NURTURE trial, but there were variations to note in the CHERISH and CS3A studies. NURTURE planned to enrol 25 patients for a treatment duration of 111 weeks, CHERISH planned to enrol 126 patients for a treatment period of 9 months and a follow-up in 3 months, while CS3A planned to enrol 20 patients for a period of 1,261 days (3.45 years).

Patients enrolled in the NURTURE trial were presymptomatic with no symptoms, and the average age was 20.5 days (SD 11.41) with 45% females. Patients enrolled in the NURTURE trial had already achieved some motor milestones according to the Hammersmith Infant Neurological Examination (HINE) Section 2 and were otherwise healthy. Almost two-thirds of the patients (65%) had two copies of the SMN2 gene and the rest had three copies. Patients enrolled in CS3A, on the other hand, had a mean age at screening of 140 days (SD 60), were 44% females, and had a mean time since diagnosis of 80 days (SD 49). The majority of the patients (81%) had two copies of the SMN 2 gene, 13% had three copies, and one was unknown. The majority of the patients in the CS3A trial (88%) displayed some form of motor function delay. The CHERISH study randomized patients in a 2:1 ratio to nusinersen and sham procedure, respectively. Overall, the distribution of baseline characteristics was similar between the two groups with an average age of 3.8 years (1.6 SD) in both groups, 88% having three copies of the SMN2 gene in both groups, and an average age of symptom onset of approximately 11 months in both groups. Although the inclusion criteria specified for the CHERISH study was for patients up

to 12 years of age, most patients were below 6 years of age (84%). The details of age distribution of patients enrolled in the CHERISH trial is displayed in Table 12. In all three trials, concomitant medication was allowed as per clinical judgment. The only prohibited medications were experimental treatments of SMA.

Patients in the NURTURE trial were administered nusinersen according to the described Health Canada–approved product monograph. CS3A had two cohorts: one received 6 mg nusinersen and one received 12 mg nusinersen according to a dosing schedule that differed from the recommendation in the prescribed Health Canada–approved product monograph. Likewise, the administration of nusinersen 12 mg in the CHERISH trial administered 12 mg nusinersen in a manner that differed from the recommendation in the Health Canada–approved product monograph. All nusinersen treatment in the three trials was administered intrathecally through lumbar puncture. Patients receiving the sham procedure in the CHERISH trial underwent a needle prick on the site of the lumbar puncture that was covered by the same bandage to maintain blinding. Administration of the procedure was conducted by unblinded personnel with no other involvement in the trial. Psychometric properties of the outcomes assessed in each trial are described in Appendix 5.

The CHERISH trial was prematurely concluded due to ethical reasons arising from the positive results generated from the interim analysis. There were no patients who discontinued treatment due to adverse events in the NURTURE or CHERISH trials; five patients discontinued treatment in the CS3A trial (four due to death and one due to withdrawal of consent).

Results from all three studies indicate an increase in the motor milestones gained in patients treated with nusinersen during the period covered in each study (183 days to 505 days). In contrast, the CHERISH trial showed regression in the motor milestones of patients allocated to the sham procedure during a period of 15 months, although the statistically significant differences captured in the HFMSE outcome was not reflected in the WHO motor milestone outcome. The CHERISH trial also provided quality of life measures for patients and their caregivers, and reported no statistically significant differences between groups. No patients died in the NURTURE trial or required ventilation, none in the CHERISH trial, and two patients in the 12 mg cohort died in CS3A and two required permanent ventilation. [redacted]

[redacted]

[redacted]

Table 12: Distribution of Age in the CHERISH Trial

	CHERISH		
	Control	**Nusinersen**	**Total**
Number of patients, N (ITT set)	42	84	126
Age (yrs)			
2	19 (45)	22 (26)	41 (33)
3	6 (14)	18 (21)	24 (19)
4	9 (21)	23 (27)	32 (25)
5	2 (5)	7 (8)	9 (7)
< 6	36 (86)	70 (83)	106 (84)
≥ 6	6 (14)	14 (17)	20 (16)

ITT = intention-to-treat; N = total number of patients; yrs = years.

Source: Clinical study report: ISIS 396443-CS4.[31]

Table 13: Patient Disposition

	NURTURE	CHERISH		CS3A
	Nusinersen	**Nusinersen**	**Control**	**Nusinersen**
Screened, N	25	179		23
Randomized, N (%)	NA – enrolled 20	84	42	NA – enrolled 21
Discontinued, N (%)	0	0	0	5 (24)
Due to fatal adverse event, N (%)	0	0	0	4 (19)
Due to non-fatal adverse event, N (%)	0	0	0	0
Due to consent withdrawal, N (%)	0	0	0	1 (5)
ITT, N	20 (100)	84 (100)	42 (100)	NR
Interim efficacy set, N (%)	NR	35 (42)	19 (45)	NR
Efficacy set, N (%)	18 (90)	66 (79)	34 (81)	NR
Evaluable population, N (%)	NR	NR	NR	19 (91)
PP, N	NR	84 (100)	42 (100)	NR
Safety, N	NR	84 (100)	42 (100)	20 (95)

ITT = intention-to-treat; N = total number of patients; NA = not applicable; NR = not reported; PP = per-protocol.

Source: Clinical study report: ISIS 396443-CS4, Progress report: 232SM202, and Clinical study report: ISIS 396443-CS3A.[30-32]

Table 14: Exposure to Study Treatments

	NURTURE	CHERISH		CS3A
	Nusinersen	Nusinersen	Control	Nusinersen
Number of patients, N	20	84	42	16 (Cohort 2)
Number of doses or sham procedures received, mean (SD)	5.4 (1.54)	4.0 (0.1)	4	6 (2)
Total amount of drug received (mg), mean (SD)	54.1 (16.1)	47.8 (1.31)	NA	67.8 (22.4)
Time on study (days), mean (SD)	293.2 (148.5)	440.6 (30.0)	443.5 (24.0)	593 (256)
Total number of patient-years	16.1	101.3	51.0	26.0

mg = milligrams; N = total number of patients; SD = standard deviation

Source: Clinical study report: ISIS 396443-CS4, Progress report: 232SM202, and Clinical study report: ISIS 396443-CS3A.[30-32]

Results

Table 15: Efficacy Outcomes

	NURTURE	CHERISH		CS3A
HINE	Nusinersen	Nusinersen	Control	Nusinersen
Number of pts, N	16	NA	NA	12 (Cohort 2)
Assessment time point (study day)	183	NA	NA	505
Motor milestone responders (Improvement of any HINE categories in which there are more categories with improvement than with worsening), N (%)	16 (100)	NA	NA	NA
Baseline mean of score, mean (SD)	NA	NA	NA	2.3 (2.7)
Assessment visit mean score, mean (SD)	NA	NA	NA	8.4 (6.8)
Change from baseline, mean (SD)	NA	NA	NA	5.8 (4.5)
HFMSE				
Number of pts, N	NA	84	42	NA
Assessment time point (month)	NA	15	15	NA
Number of pts with observed value	NA	35 (42)	19 (45)	NA
Number of pts with imputed value	NA	49 (58)	23 (55)	NA
Baseline HFMSE score, mean (SD)	NA	22.4 (8.3)	19.9 (7.2)	NA
Assessment HFMSE score, mean (SD)	NA	NA	NA	NA
Change in HFMSE, least squares mean (95% CI)	NA	4.0 (2.9 to 5.1)	–1.9 (–3.8 to 0.0)	NA
Least squares mean difference (95% CI)	NA	5.9 (3.7 to 8.1)		NA
P value	NA	< 0.0001		NA
CHOP INTEND				
Number of pts, N	16	NA	NA	13 (Cohort 2)
Assessment time point (study day)	183	NA	NA	253
Baseline CHOP INTEND score, mean (SD)	50.9	NA	NA	30.3 (11.5)
Assessment CHOP INTEND score, mean (SD)	59.9 (4.7)	NA	NA	38.5 (11.7)

	NURTURE	CHERISH		CS3A
Change from baseline, mean (SD)	8.9 (6.3)	NA	NA	8.3 (8.1)
Change from baseline in total score improved ≥ 4 points, n (%)	13 (81)	NA	NA	10/16 (62.5)
RULM				
Number of pts, N	NA	84	42	NA
Assessment time point (month)	NA	15	15	NA
Number of pts with observed value, n (%)	NA	66 (79)	34 (81)	NA
Number of pts with imputed value, n (%)	NA	18 (21)	8 (19)	NA
Baseline RULM score, mean (SD)	NA	19.4 (6.2)	18.4 (5.7)	NA
Assessment RULM score, mean (SD)	NA	NA	NA	NA
Change from baseline, mean (SD), LSM (95% CI)	NA	4.2 (3.4 to 5.0)	0.5 (–0.6 to 1.6)	NA
Difference in LSM, (95% CI)	NA	3.7 (2.3 to 5.0)		NA
P value	NA	< 0.0001		NA
WHO Motor Milestones				
Number of pts, N	16	66	34	NA
Assessment time point (study day)	183	15	15	NA
Number of pts with observed value, n (%)	NA	NA	NA	NA
Number of pts with imputed value, n (%)	NA	NA	NA	NA
Baseline WHO Motor Milestones score, mean (SD)	0 (0)	1.4 (0.9)	1.5 (0.9)	NA
Assessment WHO Motor Milestones score, mean (SD)	0.8 (0.8)	NA	NA	NA
Number of responders	NA	13 (19.7)	2 (5.9)	NA
Difference in proportion, (95% CI)	NA	13.8 (–6.6 to 34.2)		NA
P value	NA	0.0811		NA
Time to death or respiratory intervention				
Number of pts, N	18	NA	NA	NA
Number of pts who died or required respiratory intervention, n (%)	0	NA	NA	NA
Time to death or permanent ventilation				
Number of pts, N	NA	NA	NA	15 (cohort 2)
Number of pts who died or required permanent ventilation, n (%)	NA	NA	NA	4 (27)
Estimated proportion of pts who died or required permanent ventilation by:				
Day 91 (13 wks/3 mos)	NA	NA	NA	0
Day 182 (26 wks/6 mos)	NA	NA	NA	0.07
Day 273 (39 wks/9 mos)	NA	NA	NA	0.13
Day 364 (52 wks/12 mos)	NA	NA	NA	0.20
Day 394 (13 mos)	NA	NA	NA	NA
Day 455 (65 wks/15 mos)	NA	NA	NA	0.20
Day 546 (78 wks/18 mos)	NA	NA	NA	0.27

	NURTURE	CHERISH		CS3A
Day 637 (91 wks/21 mos)	NA	NA	NA	0.27
Day 728 (104 wks/24 mos)	NA	NA	NA	0.27
Hazard ratio (95% CI)	NA	NA	NA	NA
P value	NA	NA	NA	NA
Overall survival				
Number of pts, N	18	84	42	15 (cohort 2)
Number of pts who died	0	0	0	2 (13)
Estimated proportion of pts who died by:				
Day 91 (13 wks/3 mos)	NA	NA	NA	0
Day 182 (26 wks/6 mos)	NA	NA	NA	0.7
Day 273 (39 wks/9 mos)	NA	NA	NA	0.7
Day 364 (52 wks/12 mos)	NA	NA	NA	0.13
Day 394 (13 mos)	NA	NA	NA	NA
Day 455 (65 wks/15 mos)	NA	NA	NA	0.13
Day 546 (78 wks/18 mos)	NA	NA	NA	0.13
Day 637 (91 wks/21 mos)	NA	NA	NA	0.13
Day 728 (104 wks/24 mos)	NA	NA	NA	0.13
Hazard ratio (95% CI)	NA	NA	NA	NA
P value	NA	NA	NA	NA
Permanent ventilation				
Number of pts, N	18	NA	NA	15 (cohort 2)
Number of pts who required permanent ventilation	0	NA	NA	2 (13)
Estimated proportion of pts required permanent ventilation by:				
Day 91 (13 wks/3 mos)	NA	NA	NA	NA
Day 182 (26 wks/6 mos)	NA	NA	NA	NA
Day 273 (39 wks/9 mos)	NA	NA	NA	NA
Day 364 (52 wks/12 mos)	NA	NA	NA	NA
Day 394 (13 mos)	NA	NA	NA	NA
Day 455 (65 wks/15 mos)	NA	NA	NA	NA
Day 546 (78 wks/18 mos)	NA	NA	NA	NA
Day 637 (91 wks/21 mos)	NA	NA	NA	NA
Day 728 (104 wks/24 mos)	NA	NA	NA	NA
Hazard ratio (95% CI)	NA	NA	NA	NA
P value	NA	NA	NA	NA
Growth parameters				
Growth failure defined as post-baseline weight below the fifth percentile				
Number of evaluated pts, N	16	NA	NA	NA
Assessment time point	Day 183	NA	NA	NA
Number of pts with growth failure, n (%)	2 (13)	NA	NA	NA
Odds ratio (95% CI)	NA	NA	NA	NA
P value	NA	NA	NA	NA
Growth failure defined as a weight dropping ≥ 2 major percentiles in 6 mos	NA			
Number of evaluated pts, N	NA	NA	NA	NA

	NURTURE	CHERISH		CS3A
Assessment time point	NA	NA	NA	NA
Number of pts with growth failure, n (%)	4 (25)	NA	NA	NA
Odds ratio (95% CI)	NA	NA	NA	NA
P value	NA	NA	NA	NA
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Examination; LSM = least squares mean; mos = months; N = total number of pts; n = number of pts in subgroup; NA = not applicable; pts = patients; RULM = Revised Upper Limb Module; SD = standard deviation; WHO = World Health Organization; wks = weeks.

Source: Clinical study report: ISIS 396443-CS4, Progress report: 232SM202, and Clinical study report: ISIS 396443-CS3A.[30-32]

Table 16: Harms

	NURTURE	ENDEAR		CHERISH		CS3A
AEs	**Nusinersen**	**Nusinersen**	**Control**	**Nusinersen**	**Control**	**Nusinersen**
Patients with > 0 AEs, N (%)	16 (80)	77 (96)	40 (98)	78 (93)	42 (100)	20 (100)
SAEs						
Patients with > 0 SAEs, N (%)	6 (30)	61 (76)	39 (95)	14 (17)	12 (29)	16 (80)
WDAE						
WDAE, N (%)	0	13 (16)	16 (39)	0	0	4 (20)
Deaths						
Number of deaths, N (%)	0	13 (16)	16 (39)	0	0	4 (20)

AE = adverse event; N = total number of patients; SAE = serious adverse event; WDAE = withdrawals due to adverse events.

Source: Clinical study report: ISIS 396443-CS4, Progress report: 232SM202, and Clinical study report: ISIS 396443-CS3A.[30-32]

Limitations

NURTURE and CS3A were single-arm descriptive studies with no control groups. This design precludes the ability to make any statistical inference from the observed results of the studies. In addition, the lack of a control arm introduces uncertainty regarding the extent of the effect of potential covariates. The CHERISH study randomized patients using a central randomization procedure through a voice interactive system, was double-blinded with a sham procedure, and measured relevant clinical outcomes. Limitations of the CHERISH study are similar to the limitations outlined for the ENDEAR study, in addition to the limited generalizability of the results due to the difference in the treatment regimen of nusinersen from the Health Canada–approved product monograph.

Conclusions

These three trials provide additional clinical evidence of the potential efficacy and safety of nusinersen treatment in patients who are likely to develop SMA type I and type II. Efficacy results from the supportive evidence is limited in generalizability due to either study design (single-arm, non-comparative, descriptive, or phase II), or different treatment regimen or dose, or a combination of both factors. Presymptomatic patients who received nusinersen treatment in the NURTURE trial showed no fatalities after six months of assessment. CS3A reported that patients with infantile-onset symptomatic SMA show improvement in motor milestone development while treated with nusinersen; two patients (13%) died in the period of the study (728 days). In the CHERISH trial, nusinersen-treated patients with childhood-onset SMA exhibited a statistically significant gain in motor function compared with patients in the sham control group.

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Hammersmith Infant Neuromuscular Examination (HINE) Section 2: Motor Milestones;
- World Health Organization (WHO) Motor Milestones;
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND);
- Hammersmith Functional Motor Scale - Expanded (HFMSE);
- Revised Upper Limb Module (RULM);
- Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and 3.0 Neuromuscular Module;
- Assessment of Caregiver Experience in Neuromuscular Disease (ACEND).

Findings

Hammersmith Infant Neuromuscular Examination (HINE) Section 2: Motor Milestones

The HINE was based on a previous neurologic assessment and is meant for use in infants between 2 months and 24 months of age.[18] It contains three sections which assess neurologic signs (section 1), development of motor function (Section 2), and state of behaviour (section 3). The items in sections 1 and 3 can be assigned scores on an ordinal scale based on descriptive ratings and the scores can be summed to give section scores. Section 2 is composed of eight milestones: head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking.[18] Each milestone has three to five possible descriptive ratings, ranging from not performing the task at all to fully demonstrating the milestone.[18] The items can be either reported by the caretaker or observed by the examiner,[18] though information regarding inter-rater reliability between caretakers and examiners was not found. Unlike the other sections of the HINE, the Motor Milestones are age-dependent and are not intended to produce a total score.[18] Rating distributions are available for normal infants aged 12 months and 18 months for sections 1 and 2.[18]

For most individual ratings for each motor milestone in Section 2, a typical age of achievement in normal infants is provided.[18]

Head control:

- Unable to maintain head upright, normal at < 3 months
- Wobbles, normal at 4 months
- All the time maintained upright, normal at 5 months

Sitting:

- Cannot sit
- With support, normal at 4 months
- Props, normal at 6 months
- Stable sit, normal at 7 months

- Pivots, normal at 10 months

Voluntary grasp:

- No grasp
- Uses whole hand
- Index finger and thumb but immature grasp
- Pincer grasp

Ability to kick (in supine):

- No kicking
- Horizontally; legs do not lift
- Upward (vertically), normal at 3 months
- Touches leg, normal at 4 to 5 months
- Touches toes, normal at 5 to 6 months

Rolling:

- No rolling
- Rolling to side, normal at 4 months
- Prone to supine or supine to prone, normal at 6 months
- Supine to prone and prone to supine, normal at 7 months

Crawling:

- Does not lift head
- On elbow, normal at 3 months
- On outstretched hand, normal at 4 to 5 months
- Crawling flat on abdomen, normal at 8 months
- Crawling on hands and knees, normal at 10 months

Standing:

- Does not support weight
- Supports weight, normal at 4 to 5 months
- Stands with support, normal at 8 months
- Stands unaided, normal at 12 months

Walking:

- Bouncing, normal at 6 months
- Cruising (walks holding on), normal at 11 months
- Walking, normal at 15 months

Natural history for the HINE Section 2 assessment was examined in infants with type I SMA with disease onset between one to eight months of age.[19] Over a period of about four years, retrospective data from patients were analyzed if the patients received at least two

assessments occurring every two to three months until 12 months of age and every six months thereafter.[19] Although the original HINE developers did not define a quantitative scoring system for Section 2, scores for each milestone were obtained by assigning a value of 0 to the absence of the activity and adding 1 point for each incremental rating.[19] All patients with SMA type IA (disease onset at birth, n = 7) had a score of 0 for every milestone at every assessment.[19] The highest score on any item was 1 and, with the exception of one infant improving from 0 to 1 on ability to kick, none of the infants' scores improved over time.[19] Infants with SMA type IB (disease onset before three months of age, n = 24) had a score of 1 for at least one assessment for the following milestones: head control (n = 11), voluntary grasp (n = 17), and ability to kick (n = 13).[19] Both infants with SMA type IC (disease onset between three and six months of age) maintained a score of 1 for head control, voluntary grasp, and ability to kick.[19] The results imply that a score of more than 1 on any milestone is not expected in SMA type I patients.

Reliability and convergent validity of the HINE Section 2 in SMA type I were assessed in patients enrolled in the CS3A trial and who were administered nusinersen.[24] Although not described, it is assumed that a total HINE score for Section 2 was calculated by scoring each milestone on an ordinal scale (with 0 representing no ability) and summing the scores. Assessments within 14 days of each other demonstrated a test-retest reliability that was above 0.7[34] and therefore adequate (Pearson correlation coefficient $r = 0.987$, $P < 0.0001$, n = 19).[24] Change in the HINE Section 2 score from baseline (1 to 7 months of age) to last assessment (5 to 39 months of age) was moderately correlated with change in the CHOP INTEND score ($r = 0.691$, $P = 0.001$) and ulnar compound muscle action potential (CMAP) amplitude ($r = 0.511$, $P = 0.025$).[24] Hypotheses on the strength of correlations with CHOP INTEND and CMAP were not given.[24] Incremental improvements in individual items were observed in 16 of the 19 infants and were spread out across all the milestones, suggesting responsiveness to intervention with nusinersen; however, no responsiveness statistics were calculated, nor was the relative responsiveness of the HINE versus the CHOP INTEND score or ulnar CMAP amplitude.[24]

World Health Organization (WHO) Motor Milestones

The WHO Motor Milestones are a set of six milestones considered to be universal and fundamental to acquiring the ability to walk independently.[35] The milestones are: sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, and walking alone.[35] Children will typically progress sequentially through this order of milestones with the exception of crawling.[35] An international study conducted in Ghana, India, Norway, Oman, and the US, recorded ages of achievement of each milestone in healthy children between 4 months and 24 months of age, providing windows of achievement representing the 1st to 99th percentiles as follows:[35]

- Sitting without support: 3.8 months to 9.2 months
- Standing without assistance: 4.8 months to 11.4 months
- Hands-and-knees crawling: 5.2 months to 13.5 months
- Walking with assistance: 5.9 months to 13.7 months
- Standing alone: 6.9 months to 16.9 months
- Walking alone: 8.2 months to 17.6 months

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

The CHOP INTEND was developed in SMA type I infants and designed to measure motor function in infants and children with neuromuscular disorders having an infant's repertoire of motor skills.[21] It is well tolerated by infants in the target population[21,26] and can be administered to patients on non-invasive or invasive ventilation.[36] It is made up of 16 items, each rated 0 to 4 (no response, minimal, partial, nearly full, and complete level of response) giving a maximum total score of 64 when summed.[21] A higher score indicates more advanced motor development.[21] An initial pool of items, consisting of newly designed items and items taken from two previous motor scales, was evaluated in 26 infants with type I SMA.[21] The study investigators examined all items for clinical utility and redundancy while statistics describing score distributions and internal consistency (Cronbach's alpha) guided item selection.[21] An expert panel selected and edited the final item set.[21]

Intra-rater reliability assessed by a single evaluator over a two-month period in nine infants with type I SMA was acceptable according to the 0.7 threshold[34] (intraclass correlation coefficient [ICC] [3,1] = 0.96).[21] Inter-rater reliability assessed by multiple evaluators reviewing video footage of a single evaluator was also acceptable in both infants with neuromuscular diseases (ICC [3,4] = 0.98) and typically developing infants (ICC [3,5] = 0.93).[21]

Construct validity of the CHOP INTEND was established using known group comparisons in a separate study in 27 patients with type IB and IC SMA (mean age of 4 years, age range of 3.8 to 260 months).[26] CHOP INTEND score had moderate negative associations with age (Pearson correlation coefficient $r = –0.51$, $P = 0.007$) and months since symptom onset ($r = –0.49$, $P = 0.005$).[26] Patients on non-invasive ventilation with bi-level positive airway pressure (BiPAP) had lower scores than patients not requiring BiPAP (15.2 ± 10.2 versus 31.2 ± 4.2, $P < 0.001$).[26] There were no significant correlations with electrophysiological measures.[26] A separate study established convergent validity by examining motor function outcomes in 23 infants with type I SMA and 14 healthy control infants.[27] CHOP INTEND scores were compared between groups and against the Test of Infant Motor Performance Screening Items (TIMPSI), an instrument previously validated in type I SMA patients.[27] A hypothesis was not provided regarding the strength of the correlation between the two measures. Mean CHOP INTEND score was significantly lower in SMA infants compared with the control group (21.4 ± 9.6 versus 50.1 ± 10.2, $P < 0.01$).[27] In both groups, there was a strong ($r > 0.80$) positive association between CHOP INTEND and TIMPSI scores (SMA group: $r = 0.855$, $P < 0.0001$, n = 22; control group: $r = 0.839$, $P = 0.005$, n = 9).[27]

CHOP INTEND scores were studied over time in 17 type I SMA patients over a period of up to 36 months.[36] Scores were found to decrease over time at a mean rate of 1.27 points per year.[36] A minimal clinically important difference (MCID) was not found for the CHOP INTEND score.

Hammersmith Functional Motor Scale – Expanded (HFMSE)

The Hammersmith Functional Motor Scale (HFMS) was designed to measure motor function in SMA type II and III patients with limited mobility.[37] The HFMSE builds upon the HFMS by adding 13 items from the Gross Motor Function Measure (GMFM), an instrument designed for patients with cerebral palsy and previously validated in children with SMA.[37] The HFMSE is intended for use in type II and III SMA patients and captures higher

functioning skills.[37] It consists of 33 activities that can be scored one of three ways: 0 for unable to perform, 1 for performs with modification/adaptation, and 2 for performs without modification.[37] The item scores are summed to give a total score with a maximum of 66.[37] The higher the total score, the greater the patient's motor functioning.[37]

Clinical evaluators deemed the items added from the GMFM to be clinically meaningful and focus groups and interviews established content validity of all of the HFMSE items.[38,39] Focus groups with caregivers (n = 30) and patients (n = 25) of SMA types II and III were able to relate each item to at least one relevant activity of daily living.[38] A similar sample of patients and caregivers indicated in focus groups and interviews that the items on HFMSE were relevant to their life and that improvements in any of the items would translate to greater independence.[39]

Construct validity was assessed using both convergent validity and known group comparisons in two studies in patients with types II and III SMA and ages ranging from 2 years to 45 years.[37,40] Hypotheses regarding the strength of correlations with other measures were not stated. HFMSE score had strong (Spearman rank correlation coefficient $\rho > 0.80$) positive associations with the GMFM (both with and without the items that were added to the HFMSE), as well as a simple,10-point functional rating score ranging from "unable to sit" to "age-appropriate in motor skills" (ρ ranging from 0.88 to 0.98).[37,40] Further convergent validity was established through positive correlations with forced vital capacity as a percentage of predicted normal value ($\rho = 0.98$), knee flexion and extension strength (Pearson correlation coefficient $r = 0.74$ for both), and elbow flexion strength ($r = 0.77$).[40] Known group comparisons showed significant differences in median HFMSE score between those receiving BiPAP for less than and greater than 8 hours per day (23 versus 3, $P < 0.0001$), those who are able and unable to walk (52 versus 8, $P < 0.0001$), and those who have type II and III SMA (49 versus 8, $P < 0.0001$).[40] There were also significant differences in median scores between patients with differing numbers of copies of the SMN2 gene (Kruskal-Wallis test: $P = 0.0007$).[40]

Reliability and change over time were also studied. The HFMSE demonstrated adequate test-retest reliability when administered two months apart in SMA type II and III patients (ICC = 0.98).[40] A natural history study measured HFMSE score over time in SMA type II and III patients (n = 268, age range of 2.5 to 55.5 years).[41] More than 75% of the patients had a change in score from baseline to 12 months of –2 to +2 points.[41] Only 7.84% experienced an increase of more than 2 points, and this was most likely to occur in children below 5 years of age.[41] Focus groups and interviews with patients, parents, and clinicians representing SMA types I to III revealed that increases in the HFMSE scale as little as 1 point would represent meaningful change and that the scale increments may not be sensitive enough to capture small functional changes that are noticeable to patients.[39]

Revised Upper Limb Module (RULM)

The original Upper Limb Module (ULM) was designed to capture upper limb function in non-ambulatory SMA patients, especially in young children, and was previously validated in this population.[42] Due to ceiling effects, it was revised and renamed to the RULM. Some items in the RULM were incorporated from other upper limb scales, particularly the Performance of Upper Limb scale for Duchenne muscular dystrophy.[42] The RULM is well tolerated, even in young children, with a test duration of 5 to 20 minutes.[42] It consists of 19 items reflecting different functional domains that are graded on a 3-point scale.[42] With the exception of one activity with a binary score, the possible scores are: 0 (unable), 1 (able, with modification),

and 2 (able, no difficulty), giving a maximum total score of 38. The patient chooses one arm with which to perform the tasks.[42]

Adequate inter-rater reliability was established using three video assessments of the RULM that were evaluated by 17 physiotherapists (ICC = 0.928).[42] Rasch analysis was conducted on RULM assessments of 134 ambulatory and non-ambulatory SMA patients aged 2 years to 52 years (median age of 9 years). Item and person locations revealed no floor or ceiling effects and only small gaps in measurement accuracy.[42] The threshold map indicated that response categories for each item functioned as intended.[42] The Person Separation Index (PSI), an indicator analogous to Cronbach's alpha that assesses the ability of a set of items to separate the sample[43], demonstrated adequate internal consistency reliability (0.954).[42] Indicators of fit demonstrated that the observed data overall did not differ from the expected responses as predicted by the Rasch model and that total RULM score is a suitable measurement of a single concept.[42,43] Two pairs of items had correlated residuals, but their presence did not inflate the PSI. Scale performance did not differ between genders, though it was not tested for groups expected to score differently.[42]

Associations with other measures of motor function, test-retest reliability, and a minimal clinically important difference (MCID) were not found for the RULM.

Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and 3.0 Neuromuscular Module

The PedsQL Generic Core Scales are intended to be administered in both healthy and patient pediatric populations and, together with disease-specific modules, measure pediatric health-related quality of life.[25] Both the Generic Core Scales and Neuromuscular Module are available in formats for child self-report and parent proxy-report for ages 5 to 7 years, 8 to 12 years, and 13 to 18 years, along with a parent proxy-report format for ages 2 to 4.[25] Each item is scored on a 5-point Likert scale (3-point scale for ages 2 to 4) with each score linearly transformed to a scale of 0 to 100.[25] To generate domain and total scores, the transformed item scores are summed and then divided by the number of items.[25] The Psychosocial Health Summary Score is the sum of the items in the Emotional, Social, and School Functioning Scales.[25] Higher scores indicate better health-related quality of life.[25] The Generic Core Scales consist of the following scales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items).[25] The Neuromuscular Module has the following scales: About My/My Child's Neuromuscular Disease (17 items), Communication (3 items), and About Our Family Resources (5 items).[25] The Communication and About Our Family Resources scales are not available for the 5 to 7-year-old format due to insufficient consistency.[25]

The Neuromuscular Module was developed particularly for SMA and Duchenne muscular dystrophy using literature, feedback from health care providers, and focus groups consisting of patients and family members of patients.[25] It was validated in a pool of 176 children with SMA (average age of 8.53 years) across multiple centres in North America.[25] Internal consistency was acceptable (Cronbach's alpha ≥ 0.7[34]) in all the scale and summary scores for all formats of the Generic Core Scales (0.64 to 0.86) and Neuromuscular Module (0.77 to 0.91) except for Social Functioning on the self- and proxy-report formats and Emotional and School Functioning on the self-report format.[25]

Construct validity for the Generic Core Scales was established using the known-groups method in SMA patients and a healthy children sample derived from previous data.[25] The scale and summary scores were higher in healthy children with mostly large effect sizes

(range: 0.74 to 3.26).[25] The Physical Functioning scale related to mobility status with scores increasing from non-sitter to sitter to walker.[25] In the Neuromuscular Module, scores for About My Neuromuscular Disease for both formats and Total Score and About Our Family Resources for proxy-report increased with greater mobility.[25]

Test-retest reliability was determined in a set of 60 SMA patients with an average of 29.85 days between assessments.[25] There was a wide range in agreement in all the Generic Core Scales (ICC range: 0.72 to 0.84 for self-report, 0.34 to 0.79 for proxy-report) and Neuromuscular Module (ICC range: 0.58 to 0.84 for self-report, 0.82 to 0.90 for parent-report) scales in the self- and proxy-report formats, with the exception of Physical Health in the Generic Core Scales on the parent proxy-report format (ICC = 0.34).[25] The summary scores had adequate test-retest reliability except for the proxy-report total score for the Generic Core Scales.[25] Similar results for the Neuromuscular Module scales and total score were obtained in a separate set of 33 SMA patients (ICC range: 0.73 to 0.84).[44]

Inter-rater reliability between child self-report and parent proxy-report was determined for the scale and summary scores.[25] Parent-child agreement ranged from poor to moderate for the Generic Core Scales (ICC range: 0.36 to 0.44) and Neuromuscular Module scales (ICC range: 0.33 to 0.48).[25]

For the total score of the Generic Core Scales in the general pediatric population, the MCIDs calculated from the score distributions were 4.4 for the self-report format and 4.5 for the proxy-report format.[45] A clear MCID was not found for the SMA population.

Assessment of Caregiver Experience in Neuromuscular Disease (ACEND)

The ACEND is a self-administered instrument for assessing caregiver impact on parents raising children severely affected by neuromuscular disease.[46] Higher scores in the ACEND represent less intense caregiving impact.[46] There are two domains: Physical Impact with the four subdomains of feeding/grooming/dressing (6 items), Sitting/play (5 items), Transfers (5 items), and Mobility (7 items) and General Caregiver Impact with the three subdomains of time (4 items), Emotion (9 items), and Finance (5 items).[46] The Physical Impact items are scored on a 6-point ordinal scale and the General Caregiver Impact items are scored on a 5-point scale.[46] These scores are used to generate domain and total scores standardized to a range of 0 to 100.[46]

Some items for the ACEND were taken from previous instruments and new items were developed with a panel of experts which included orthopedic surgeons, physical therapists, and parents of patients.[46] A total of 46 caregivers of children with moderate to severe neuromuscular disease were administered the ACEND survey and asked to rate clarity and relevance of the items.[46] All items were considered clear and relevant by the caregivers.[46] Each domain was assessed for consistency and some items may be redundant as they had high inter-item and item-total correlations.[46]

Patients were also classified according to the gross motor function classification system (GMFCS) to assess convergent validity and floor and ceiling effects of the ACEND.[46] All patients belonged to GMFCS levels III, IV, or V, implying inability to walk without mobility devices.[46] All of the total and subdomain scores decreased significantly with increasing GMFCS level (decreasing motor function), with the exception of the Finance subdomain.[46] Score distributions across GMFCS levels indicated floor or ceiling effects in all the Physical Impact subdomains and ceiling effects in two of the three General Caregiver Impact

subdomains.[46] Item distributions were considered to be adequate aside from some items in the Transfers and Mobility subdomains.[46]

The ACEND was administered to caregivers of children aged 3 years to 25 years with cerebral palsy at GMFCS levels IV and V undergoing orthopedic hip or spine surgery.[47] Although there was an increase in health-related quality of life as measured by a different instrument from pre-surgery to 12 months post-surgery, the ACEND was not sensitive to this increase (n = 44).[47] However, a multivariable model found time to be a significant predictor of ACEND total score.[47] An MCID was not found for the ACEND score and it has yet to be assessed in the SMA population.

Table 17: Validity and Minimal Clinically Important Differences of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
Hammersmith Infant Neuromuscular Examination (HINE) Section 2: Motor Milestones	A set of 8 motor milestones to assess development between the ages of 2 and 24 months, with a 3- to 5-point ordinal scale for each milestone	Yes	A score of > 1 point for any given milestone is highly unlikely in untreated SMA type I patients[19]	Haataja 1999,[18] De Sanctis 2016,[19] Bishop 2017[24]
World Health Organization (WHO) Motor Milestones	A set of 6 motor milestones with age windows of achievement of each milestone provided for normal infants	Unknown in SMA	Unknown	WHO Multi-centre Growth Reference Study Group 2006[35]
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	A set of 16 tasks to measure motor development in infants and children with neuromuscular disorders, with a 5-point ordinal scale for each item	Yes	Unknown	Glanzman 2010,[21] Glanzman 2011,[26] Finkel 2014,[36] Kolb 2016[27]
Hammersmith Functional Motor Scale—Expanded (HFMSE)	A set of 33 tasks to measure motor function in SMA type II and type III patients with limited mobility, a 3-point ordinal scale for each item	Yes	An increase of > 2 points in total score is unlikely in untreated SMA type II and III patients.[41] Patient and caregivers consider a 1-point increase meaningful.[39]	O'Hagen 2007,[37] Glanzman 2011,[40] Mercuri 2016,[41] McGraw 2017,[39] Pera 2017[38]
Revised Upper Limb Module (RULM)	A set of 19 tasks to measure motor function in non-ambulatory SMA patients, with a 3-point ordinal scale for each item	Yes (with limitations)	Unknown	Mazzone 2017[42]
Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and 3.0 Neuromuscular Module	Surveys consisting of 23 and 25 items for measuring health-related quality of life in healthy and patient pediatric populations, with a 5-point Likert scale for each item	Yes (with limitations)	Generic Core Scales in the general pediatric population: 4.4 points for self-report and 4.5 points for proxy-report Neuromuscular Module: unknown	Iannaccone 2003,[44] Varni 2003,[45] Iannoccone 2009[25]
Assessment of Caregiver Experience in Neuromuscular Disease (ACEND)	A 41-item survey for assessing caregiver impact on parents raising children severely affected by neuromuscular disease, with	Neuromuscular disease: yes (with limitations)	Unknown	Matsumoto 2011,[46] DiFazio 2016[47]

Instrument	Type	Evidence of Validity	MCID	References
	a 5- or 6-point ordinal scale for each item	SMA: unknown		

MCID = minimal clinically important difference; SMA = spinal muscular atrophy

Conclusions

The HINE Section 2: Motor Milestones and WHO Motor Milestones provide information on normal, healthy infant motor development and can be used to identify abnormalities in attainment of motor milestones.[18,35] A score can be calculated from the HINE Motor Milestones that has excellent test-retest reliability.[24] Change in the score moderately correlates with change in other measures of motor function in type I SMA patients receiving nusinersen.[24] Natural history in type I SMA patients strongly suggests that an improvement greater than one point in any milestone is highly unlikely.[19]

Functional motor scales designed to assess function in SMA patients were also used in nusinersen trials. All of the motor function scales were well tolerated in their intended populations and were developed with input from experts in neuromuscular disease. The CHOP INTEND is a set of activities assessing motor function in infants and children with neuromuscular disorders.[21] It has excellent intra-rater and inter-rater reliability[25] and its construct validity has been demonstrated in patients with type I SMA.[26,27] The HFMSE is a motor function assessment appropriate for use in more advanced SMA patients with limited mobility.[37] In types II and III SMA patients, both test-retest reliability[40] and construct validity are excellent.[37,40] Longitudinal data shows that more than 75% of type II and type III SMA patients experience a change in HFMSE score from –2 and +2 over the course of a year.[41] Patient and caregivers have indicated that the items in the HFMSE are relevant[38,39] and that an improvement of one point would be meaningful.[39] The RULM is an improved version of the ULM and is designed to measure motor function of the upper limbs in non-ambulatory SMA patients.[42] It has excellent inter-rater reliability in ambulatory and non-ambulatory SMA patients aged 2 years and up. According to Rasch analysis, the RULM measures a single concept, separates the sample well, and has no issues with floor effects, ceiling effects, or item dependence.[42] Test-retest reliability and associations with other measures of motor function were not found for the RULM. MCID were not found for any of the scales. A potential limitation of functional scales is that their scores can be affected by developmental maturation in children who gain or regain abilities after adapting to their strength limitations.[3]

The PedsQL 4.0 Generic Core Scales and 3.0 Neuromuscular Module are surveys for assessing quality of life in pediatric patients, each with multiple scales and child self-report and parent proxy-report formats.[25] There are limitations in the agreement between the self-report and proxy-report formats for all of the scales and the test-retest reliability for some of the scales.[25] Due to insufficient internal consistency, some of the Generic Core Scales should only be used for descriptive analyses.[25] Scale and summary scores differ between healthy children and SMA patients and the Physical Functioning scale and Neuromuscular Module correlate well with mobility status.[25] MCIDs of 4.4 and 4.5 for the self-report and proxy-report formats are indicated for the Generic Core Scales total score in the general pediatric population.[45] An MCID was not found for the Generic Core Scales or Neuromuscular Module in the SMA population.

The ACEND is a survey for assessing caregiver impact on parents raising children with neuromuscular disease.[46] Caregivers indicated that all items are clear and relevant.[46] All of the domain and subdomain scores (except for Finance) demonstrated convergent validity with the GMFCS in a population with various neuromuscular disorders.[46] Test-retest reliability was not assessed[46] and there may be issues with item redundancy,[46] ceiling and floor effects,[46] and responsiveness.[47] An MCID was not found for the ACEND score and the ACEND has yet to be assessed in the SMA population.

Appendix 6: Summary of Safety Data from Long-Term Studies

Objective

To provide a summary of safety data from long-term studies of nusinersen in patients with spinal muscular atrophy (SMA).

Introduction

The manufacturer provided progress reports on two additional studies in patients with SMA patients receiving nusinersen. The SHINE study is an open-label extension study for patients who previously participated in the ENDEAR, CHERISH, CS3A, and CS12 studies. The EMBRACE study is a two-part study for SMA patients not eligible for the ENDEAR or CHERISH studies with a randomized, sham-controlled part followed by an open-label extension part. Due to the observed efficacy of nusinersen in the interim analysis of one of the pivotal trials, 14 patients in the EMBRACE study ended the first part early and directly transitioned to the open-label extension part. The only end points for which results are available in the progress reports are deaths and serious adverse events (SAEs).

Table 18: Details of Included Studies

	SHINE	EMBRACE
Study Design	Phase III, multi-centre, open-label extension study for patients who previously participated in index studies CS3B (ENDEAR), CS4 (CHERISH), CS12, and CS3A	Phase II, multi-centre study for patients with SMA not eligible to participate in ENDEAR or CHERISH with two parts: • Part 1 is a randomized, double-blind, sham-controlled study • Part 2 is an open-label extension study
Locations	NR	NR
Enrolled (N)	207	21
Inclusion Criteria	Completion of the index study in accordance with the study protocol within the preceding 12 weeks	• Genetic documentation of 5q SMA homozygous gene deletion, mutation, or compound heterozygote • One of the following: ○ onset of clinical signs and symptoms consistent with SMA at ≤ 6 mos of age and documentation of 3 copies of the SMN2 gene ○ onset of clinical signs and symptoms consistent with SMA at ≤ 6 mos of age, > 7 mos of age at screening, and documentation of 2 copies of the SMN2 gene ○ onset of clinical signs and symptoms consistent with SMA at > 6 mos of age, ≤ 18 mos of age at Screening, and documentation of 2 or 3 copies of the SMN2 gene • For Part 2 only: participation in Part 1 and completion of the end of Part 1 evaluation assessments
Exclusion Criteria	• Any new condition or worsening of existing condition which in the opinion of the Investigator would make the patients unsuitable for enrolment, or could interfere with the patients participating in or completing the study	• Any previous exposure to nusinersen other than during part 1; previous dosing in this study or previous exposure in other studies with nusinersen • Signs or symptoms of SMA present at birth or within the first week after birth

	SHINE	EMBRACE
	• Treatment with another investigational agent, biological agent, or device within 1 month of Screening, or 5 half-lives of study drug, whichever is longer	• Ventilation for ≥ 16 hrs/day continuously for > 21 days at screening • Permanent tracheostomy, implanted shunt for CSF drainage, or implanted central nervous system catheter at screening • History of brain or spinal cord disease that would interfere with the lumbar puncture procedure, CSF circulation, or safety assessments • Hospitalization for surgery (e.g., scoliosis surgery), pulmonary event, or nutritional support within 2 mos prior to screening, or hospitalization for surgery planned during the study • Treatment with an investigational drug for SMA (e.g., albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, hydroxyurea), biological agent, or device within 30 days prior to screening • Any history of gene therapy, prior ASO treatment, or cell transplantation • Ongoing medical condition that according to the Investigator would interfere with the conduct and assessments of the study
Intervention	12 mg of intrathecally administered nusinersen ENDEAR: • Blinded loading phase with 4 doses on days 1, 15, 29, and 64 for ENDEAR control group and 3 sham procedures on days 1, 15, and 64, and 1 dose on day 29 for ENDEAR nusinersen group • Maintenance phase with 6 doses on days 184, 304, 424, 544, 664, and 784 CHERISH: • Blinded loading phase with 3 loading doses on days 1, 29, and 85 for CHERISH control group and 1 sham procedure on day 29 and 2 doses on days 1 and 85 for CHERISH nusinersen group • Maintenance phase with 4 doses on days 265, 445, 625, and 805 CS3A: 8 doses every 4 mos on days 1, 120, 240, 360, 480, 600, 720, and 840. CS12: 5 doses on days 1, 181, 361, 541, and 721.	12 mg of intrathecally administered nusinersen Part 1: 6 doses on days 1, 15, 29, 64, 183, and 302 Part 2 (nusinersen group from Part 1): 7 doses on days 1, 120, 239, 358, 477, 596, and 715 Part 2 (control group from Part 1): 10 doses on days 1, 15, 29, 64, 183, 302, 421, 540, 659, and 778
Phase		
Screening	≤ 21 days	28 days
Double-blind loading	ENDEAR: 183 days CHERISH: 264 days CS3A and CS12: NA	NA
Double-blind treatment	NA	10 mos (planned)

	SHINE	EMBRACE
Open-label	ENDEAR: 600 days CHERISH: 540 days CS3A: 839 days CS12: 720 days	714 or 777 days
Follow-up	ENDEAR and CS3A: 120 days CHERISH and CS12: 180 days	4 mos for both the treatment and open-label periods (planned)
Reported End Points	Death and SAEs	Death and SAEs
Planned End Points	Safety and tolerability, efficacy, and pharmacokinetics and immunogenicity	Safety and tolerability, efficacy, and pharmacokinetics and immunogenicity
Publications	None	None

ASO = antisense oligonucleotide; CSF = cerebral spinal fluid; mos = months; NA = not applicable; NR = not reported; SAE = serious adverse event; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2.

Source: Clinical study reports.[33,48]

Table 19: Summary of Baseline Characteristics

	SHINE	EMBRACE
Number of patients, N	207	21
Demographics		
Age, median (range)	4.0 (0.6 to 19.3) years	NR
Age at first dose, median (range)	NR	11.4 (7 to 53) mos
Female, n (%)	110 (53)	10 (48)
White, n (%)	171 (83)	9 (43)
Asian, n (%)	17 (8)	5 (24)
Other, n (%)	10 (5)	NR
Black or African-American, n (%)	5 (2)	0
Age at disease onset, median (range)	8.0 (0 to 60) mos	5.1 (1.8 to 11.0) mos
Age at diagnosis, median (range)	15.0 (0 to 96) mos	10.0 (5.5 to 15.0) mos
SMN2 copy number		
2 copies, n (%)	90 (43)	7 (33)
3 copies, n (%)	110 (53)	14 (67)
4 copies, n (%)	7 (3)	0
Disease symptoms (NA for CS4 and CS12)		
Hypotonia, n (%)	83 (40)	NR
Developmental motor delay, n (%)	74 (36)	NR
Paradoxical breathing, n (%)	68 (33)	NR
Pneumonia or respiratory symptoms, n (%)	26 (13)	NR
Limb weakness, n (%)	82 (40)	NR
Swallowing or feeding difficulties, n (%)	38 (18)	NR
Motor function achieved		
Ever sat without support, n (%)	124 (60)	NR
Ever stood without support, n (%)	21 (10)	NR
Ever walked with support, n (%)	36 (17)	NR
Ever walked at least 15 feet independently, n (%)	16 (8)	NR

mos = months; n = number of patients in subgroup; NA = not applicable; NR = not reported; SMN2 = survival motor neuron 2.

Source: Clinical study reports.[33,48]

Table 20: Patient Disposition

	SHINE	EMBRACE
Screened, N	228	21
Enrolled, N (%)	228 (100)	21 (100)
Safety set, N (%)	207 (91)	21 (100)
Discontinued, N (%)	2 (1)	1 (5)

N = total number of patients.

Source: Clinical study reports.[33,48]

Table 21: Exposure to Study Treatments

	SHINE	EMBRACE
Number of patients, N	207	21
Number of doses or sham procedures received, mean (SD)	2.6 (1.3)	NR
Number of doses or sham procedures received, n (%):		
1	44 (21)	0
2	86 (42)	0
3	13 (6)	0
4	44 (21)	3 (14)
5	16 (8)	9 (43)
6	4 (2)	9 (43)

N = total number of patients; n = number of patients in subgroup; NR = not reported; SD = standard deviation

Source: Clinical study reports.[33,48]

Results

In the SHINE study, 71 SAEs were reported in 38 patients. All were considered by the study investigators to be unrelated to the study treatments with the exception of one SAE that was considered unlikely to be related. There were three deaths reported and none were related to study treatment. The causes of death were: disease progression, pneumonia, and acute respiratory failure secondary to a parainfluenza virus infection.

In the EMBRACE study, 50 SAEs were reported in nine patients. All SAEs were considered by the study investigators to be unrelated to study treatment. One death was reported and was unrelated to study treatment. The cause of death was brain death following hospitalization due to respiratory distress and life-threatening cardiorespiratory arrest and hypoxic-ischemic encephalopathy.

Most SAEs from the progress reports for SHINE and EMBRACE were respiratory in nature and consistent with the natural history of SMA.

Table 22: Summary of Serious Adverse Events

	SHINE N = 207	EMBRACE N = 21
Patients reporting > 0 SAEs, n (%)	38 (18)	9 (43)
Total number of SAEs	71	50
Common SAEs (> 5% of all SAEs in at least one study), n (%)		
Acute respiratory failure	8 (11.2)	4 (8)
Apnea	4 (5.6)	0
Pneumonia	10 (14.1)	7 (14)
Pneumonia (bacterial or viral)	5 (7.0)	2 (4)
Respiratory distress	4 (5.6)	6 (12)
Respiratory failure	0	3 (6)
Respiratory syncytial virus infection	0	3 (6)
Respiratory tract infection	2 (2.8)	3 (6)
Rhinovirus infection	4 (5.6)	4 (8)
Upper respiratory tract infection	5 (7.0)	0
Additional SAEs of special interest, n (%)		
Adenovirus or viral infection	2 (2.8)	0
Atelectasis	1 (1.4)	0
Bronchiolitis	1 (1.4)	1 (2)
Bronchitis	2 (2.8)	0
Lower respiratory tract infection	2 (2.8)	1 (2)
Parainfluenzae virus infection	2 (2.8)	1 (2)
Pneumonia (aspiration)	2 (2.8)	2 (4)

N = total number of patients; n = number of patients in subgroup; SAE = serious adverse event.

Source: Clinical study reports.[33,48]

Limitations

The two extension studies were single-arm, open-label studies. The design of the studies provides only descriptive results with the inability for statistical inferences. The lack of control groups allows the influence of potential covariates. Considering the lifelong nature of the disease, additional information regarding the sustainability of efficacy and continuous safety and tolerability beyond these extension studies is needed.

Conclusions

Two extension studies (SHINE and EMBRACE) provide additional data to assess the safety of nusinersen. The deaths and SAEs reported in the two open-label extension studies were mostly respiratory in nature, consistent with the natural history of SMA, and were considered to be unrelated to study treatment.

Table 23: Numbers of Serious Adverse Events

	SHINE N = 207	EMBRACE N = 21
Patients reporting > 0 SAEs, n (%)	38 (18)	9 (43)
Total number of SAEs	71	50
Most common SAEs (> 5% of all SAEs), n		
Acute respiratory failure		
Recovered/resolved	6	4
Fatal	1	0
Unknown	1	0
Respiratory failure		
Recovered/resolved	0	2
Not recovered/resolved	0	1
Respiratory distress		
Recovered/resolved	4	5
Not recovered/not resolved	0	1
Pneumonia		
Recovered/resolved	5	3
Recovered/resolved with sequelae	1	2
Not recovered/not resolved	2	1
Fatal	1	0
Unknown	1	1
Pneumonia aspiration		
Recovered/resolved	1	2
Not recovered/not resolved	1	0
Pneumonia bacterial, recovered/resolved	1	1
Pneumonia respiratory syncytial viral, unknown	1	0
Pneumonia viral		
Recovered/resolved	2	1
Recovered/resolved with sequelae	1	0
Lower respiratory tract infection		
Recovered/resolved	1	1
Not recovered/not resolved	1	0
Upper respiratory tract infection		
Recovered/resolved	3	0
Not recovered/not resolved	2	0
Respiratory tract infection		
Recovered/resolved	1	1
Recovered/resolved with sequelae	0	1
Not recovered/not resolved	1	1
Adenovirus or viral infection, recovered/resolved	2	0
Bronchitis, recovered/resolved	2	0
Bronchiolitis, recovered/resolved	1	1
Parainfluenzae virus infection		
Recovered/resolved	1	1
Not recovered/not resolved	1	0
Respiratory syncytial virus infection		
Recovered/resolved	0	2

	SHINE N = 207	EMBRACE N = 21
Not recovered/not resolved	0	1
Rhinovirus infection		
Recovered/resolved	3	3
Not recovered/not resolved	1	1
Apnea		
Recovered/resolved	3	0
Not recovered/not resolved	1	0
Atelectasis, recovered/resolved	1	0

N = total number of patients; n = number of patients in subgroup; SAE = serious adverse event.

Source: Clinical study reports.[33,48]

Appendix 7: Clinical Features, Epidemiology, Natural History, and Management of Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a severe neuromuscular disease and is the leading genetic cause of infant death.[7,8] It is characterized by the degeneration of alpha motor neurons in the anterior horn of the spinal cord, leading to progressive muscle weakness.[8] The most common form of SMA, 5q SMA, makes up more than 95% of all cases and is an autosomal recessive disorder caused by homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (SMN1) gene.[1,2] The present CADTH Common Drug Review (CDR) submission for nusinersen lists 5q SMA as the indication and 5q SMA is presently referred to as SMA. While deletion or mutation of the SMN1 gene results in SMN protein deficiency, the SMN2 gene produces a relatively small amount of functional SMN protein and SMN2 copy numbers modulate the severity of the disease.[1,7-9]

SMA is a rare disease and estimates of its incidence and prevalence vary between studies. Most of these studies relied on clinical rather than genetic diagnosis and were often performed in small cohorts based in Europe.[2] The incidence of SMA is often cited as being approximately 10 in 100,000 live births.[2] One recent review found estimates ranging from 5.0 to 24 in 100,000 births.[2] Prevalence is estimated to be approximately 1 to 2 in 100,000 persons[2] and is affected by the drastically shortened life expectancy in the most common type of SMA.

The disease first manifests in various ways, depending on age of onset. Infants present with severe hypotonia and feeding difficulties while later onset in young children may appear as difficulty with stairs and frequent falls.[14] Adult-onset SMA presents as mild proximal muscle weakness.[8] Genetic testing gives a definitive diagnosis for 5q SMA and the first step is to test for SMN 1 gene deletion.[9] If homozygous SMN1 deletion is not found, sequencing of the SMN1 coding region may identify a causative mutation.[9]

Preclinical studies have shown that SMN deficiency results in defects in multiple components of the motor system, including the motor neurons.[8] Electrophysiological studies and clinical findings in SMA patients show that patients typically experience a sharp decline in motor function with motor unit loss soon after symptom onset, followed by a long plateau period of relative stability in motor function.[3,8] According to the clinical expert, motor function decline is irreversible aside from possible gains in strength and gross motor abilities in infants still undergoing normal muscle hypertrophy in the first two years of life. Muscle weakness tends to be symmetrical, more proximal rather than distal, and more severe in the lower limbs than in the upper limbs.[9]

SMA is divided into four clinical subtypes which vary in age of onset, highest motor milestone achieved, and prognosis. While the subtypes provide a convenient means of classifying patients, it should be noted that patients exist along a continuum of disease severity with overlap in symptoms between subtypes.

Type I: These patients show symptoms before 6 months of age, never achieve the motor milestone of sitting unsupported, and generally do not survive past two years of age due to respiratory failure.[1,7-9] SMA type I is the most common type of SMA, accounting for about 60% of SMA diagnoses.[2] Almost all SMA type I patients have two or three copies of SMN2, giving rise to a broad range of phenotypes.[15] Additional subtypes of IA, IB, and IC have

been proposed based on age of onset, with IA being the earliest and most severe subtype. SMA type 0 is sometimes included in classification systems and presents in neonates as joint contractures, severe weakness and hypotonia, respiratory insufficiency, and a life expectancy of less than six months.[1,7] Muscle weakness in SMA type I is severe to the point where patients typically cannot perform antigravity limb movements and have no head control, though facial muscles are spared.[9] Fine motor skills are affected, with infants unable to grasp using their whole hand.[19] Weakness in the intercostal muscles in combination with sparing of the diaphragm leads to paradoxical breathing and a bell-shaped chest.[1,9] Bulbar weakness results in difficulty swallowing and feeding, with risk of failure to thrive and aspiration.[1,9] Reflux and impaired cough and swallowing contribute to risk of aspiration and recurrent pulmonary infections.[1,7,9] A gastrostomy tube for feeding combined with nighttime and possibly daytime non-invasive ventilation with bi-level positive airway pressure (BiPAP) can improve quality of life[1,7] and life expectancy.[49] Aggressive intervention with a tracheostomy and permanent ventilation is also possible and can prolong life expectancy; however, this is a decision to be made by the family with the support of health care providers.[1,7]

Type II: Patients with type II SMA achieve the milestone of sitting unsupported, but never walk independently. Symptoms generally appear between 6 to 18 months after birth and most patients will survive past the age of 25,[7,14] with life expectancy improved by aggressive supportive care.[14] Type II patients represent about 20% to 30% of SMA cases[2] and most SMA type II patients have three copies of SMN2.[15] In addition to the inability to walk independently, common symptoms are fine tremors of the upper extremities, tongue fasciculation, joint contractures, and scoliosis.[1,9,14] Scoliosis and weak intercostal muscles can cause restrictive lung disease.[1] There is a range in severity, with weaker patients requiring non-invasive ventilation.[9] Difficulty swallowing is less common than in type I patients and difficulty with feeding comes from masticatory muscle weakness.[9]

Type III: Type III SMA makes up about 10% to 20% of SMA cases[2] and presents between 18 months of age and adulthood. These patients are able to walk independently at some point in their life and typically have a normal life expectancy.[14] Most type III patients have three or four copies of SMN2.[15] An age of onset prior to 3 years is associated with estimated probabilities of 73%, 44%, and 34% of walking 10, 20, and 40 years after onset.[16] In those with age of onset after 3 years, the estimated probabilities are 97%, 89%, and 67% for walking 10, 20, and 40 years after onset.[16] SMA type III patients have little or no respiratory weakness.[1] Ambulatory patients may exhibit abnormal gait characteristics due to proximal weakness[14] while patients who lose the ability to walk often develop scoliosis.[9]

Type IV: A very small proportion of SMA cases are type IV or adult-onset SMA, the mildest form of the disease. Although muscle weakness is present, these patients retain the ability to walk, have a normal life expectancy, and do not suffer from respiratory or nutritional issues.[9]

Aside from nusinersen, there are currently no effective treatments for SMA and supportive care seeks to improve quality of life. Respiratory management is essential for all children with type I SMA and some with type II. Non-invasive ventilation with BiPAP can help with disordered breathing at nighttime and can be used during the day as needed for hypercapnia.[1] Secretion mobilization is also important in patients with weak cough and this can be achieved with postural drainage, assisted coughing, and oral suction.[7,9] When non-invasive ventilation is no longer sufficient, tracheostomy and permanent, invasive

ventilation is an option. However, there is no consensus in guidelines with respect to the suitability of this intervention and its implementation remains a choice for the family.[7,14] In patients with difficulty chewing and swallowing, changing food consistency can help with feeding and reduce risk of aspiration. A gastrostomy tube can also be placed, though there is no consensus on when this should occur.[14]

For gross motor function, management strategies include mobility aides, bracing, and physical therapy. Patients able to bear weight may make use of a standing frame or ankle-foot orthoses (AFOs), and physical activity such as swimming can increase stamina.[14] Manual and motorized wheelchairs provide mobility to those who can use them. Scoliosis is very common in non-ambulatory type II and type III patients and can be corrected with surgery.[14] Bracing, seating modification, and physical therapy may slow scoliosis progression in a child until they can undergo surgery.[7]

In summary, 5q SMA is a rare and often debilitating neuromuscular disease that is the leading genetic cause of infant death. The incidence of SMA is approximately 10 in 100,000 live births.[2] The homozygous deletion or deletion and mutation of the SMN1 alleles leads to irreversible and progressive decline in motor function. Variation among patients in the number of copies of the less effective SMN2 gene accounts for part of the wide spectrum of disease severity. In general, an earlier disease onset is associated with more severe symptoms and lower probability of achieving motor milestones. Patients less than six months of age at disease onset will never sit independently and will likely to die of respiratory failure before two years of age. In contrast, those with adult-onset SMA may experience muscle weakness but will have a normal life expectancy and remain ambulatory. With the exception of nusinersen, there is currently no disease-modifying therapy available.

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